PREVENTION OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM IN INJURED PATIENTS

A Trial of Anticoagulant Prophylaxis with Phenindione in Middle-aged and Elderly Patients with Fractured Necks of Femur

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THIS paper is concerned with a controlled prophylactic trial of an anticoagulant in a group of patients susceptible to venous thrombosis and pulmonary embolism. The drug, phenindione (phenylindanedione), given in effective dosage under laboratory control, prevented these complications and the prophylaxis proved practicable and safe.

Such prophylaxis in injured patients has two main bases (see Sevitt 1959):

(1) Pulmonary embolism is a relatively common cause of illness and death, particularly in those older than 50 years, confined to bed for more than a few days. It was found in about 20% of necropsies in the Birmingham Accident Hospital; it was the cause of death in 14%, and in 40–50% of elderly patients who died after a fractured femur, tibia, or pelvis.

(2) Thrombosis of deep veins of the lower limbs is common at necropsy: it was found in 60% of an unselected series of fatally injured patients *without* pulmonary embolism and in more than 80% of elderly patients who died after a fractured femur.

Thrombosis is usually a silent process: only about a third of the cases with thrombi at necropsy have had relevant symptoms or signs during life. Even when clinical evidence of thrombosis is present it is generally unilateral, while the thrombosis is usually bilateral. Symptomless thrombosis explains why embolism is often unheralded by swelling, pain, or tenderness in the lower limbs. In the present trial nearly 60% of those with fatal embolism had venous thrombosis not diagnosable clinically.

Marks et al. (1954) treated more than 1000 cases of venous thrombosis with a very low mortality from embolism, but found that the annual number of cases of fatal embolism in the hospital was apparently unaffected. Their experience emphasises the importance of silent thrombosis and the frequency of unheralded embolism. Pulmonary embolism may also strike too soon after the clinical onset of thrombosis for anticoagulant therapy to be possible or effective.

Anticoagulant Prophylaxis

It is therefore important to know whether prophylaxis with anticoagulant drugs can prevent deep-vein thrombosis and hence embolism. Prophylaxis involves giving a drug to a large number of patients to prevent venous thrombosis in all and hence the risk of thrombus detachment and embolism.

Heparin was used as a prophylactic agent and was found of great value (Murray and Best 1938, Bauer 1941, 1946, Crafoord 1941, Jorpes 1941, Wetterdall 1941), but enthusiasm was abated by the expense of the drug and the tedium of its administration. Later dicoumarol became available and was used either with or without a preliminary course of heparin (Lehmann 1943, Barker et al. 1945, Bruzelius 1945, Murray 1947, Wise et al. 1949, Baker et al. 1950, McCann 1950, Kistner and Smith 1954, Insinger 1957). These trials were not specially concerned with injured patients and were generally related to the prevention of thromboembolic incidents after major surgery or in medical cases. They were all essentially clinical in approach, noting the incidence of diagnosed venous thrombosis and pulmonary embolism in the series. Often the incidence was compared with the results of previous years and not with that of a concurrent untreated series. The patients in each series varied widely in their ages, clinical diagnoses, and activity, and no doubt in their liability to thrombosis and embolism. Thus none of the reports can be considered as a controlled trial. Neither mortality-rates nor causes of death were reported, and necropsy studies of the incidence of venous thrombosis and pulmonary embolism were not made. Nevertheless, the reports taken together indicate a definite and sometimes considerable measure of protection. Many of the failures resulted from too late, too little, or too brief administration of the drug, or from difficulties inherent in the unpredictable effects of dicoumarol or early imperfections in laboratory control of dosage.

Some of the newer drugs such as ethylbiscoumacetate and phenindione are quicker-acting than dicoumarol and are non-cumulative; laboratory control of dosage is easier, and effective anticoagulant therapy can be maintained for long periods without danger of significant hæmorrhage. These drugs are extensively used for treating clinical thrombosis and embolism.

The Trial

This was designed as a controlled clinical experiment with a concurrent study of patients divided into two main groups: (1) cases given phenindione (phenindione series) and (2) an untreated or control series.

The trial was restricted to patients over 55 years of age with either a subcapital or pertrochanteric (intertrochanteric) fracture of the femur. These were selected, first because they were known to have a high incidence of venous thrombosis and pulmonary embolism; secondly, because they are a relatively

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TABLE I—NUMBERS OF CASES ADMITTED TO THE TRIAL IN SUCCESSIVE MONTHS

Group	1957				1958												1959			Totals
	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mch	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mch	
Phenindione:																				
Series	0	4	10	5	11	8	7	9	9	7	6	6	9	8	8	12	8	14	9	150
Rejects	0	0	0	0	1	2	3	0	1	0	0	1	2	0	1	0	2	0	2	15
Control:																				
Series	1	8	8	12	8	13	11	3	5	6	9	15	5	9	7	12	13	5	0	150
Rejects	0	0	0	0	0	0	1	0	0	0	0	2	0	0	0	1	0	0	0	4
Totals	1	12	18	17	20	23	22	12	15	13	15	24	16	17	16	25	23	19	11	319

homogeneous group with single and almost "standard" injuries so that, when divided into two series, one was likely to be similar to the other in age-sex distribution, health and disease, injury, therapy, and other factors (table II); thirdly, being mostly elderly patients their relatively high fatality-rate would provide the opportunity to dissect the lower venous tree and pulmonary arteries and thereby obtain unequivocal evidence of thrombosis and embolism or their absence; and fourthly, because enough of them are admitted to the hospital to provide an answer in a reasonable period.

The trial began near the end of September, 1957, and those admitted up to March, 1959, were included; it ended in June, 1959, taking about 21 months to complete (table I). Each survivor was studied for between three and four months. 325 cases were admitted, but 6 were sent from other hospitals for the hip operation only and were sent back within a few days. This left 319 cases for the trial. Chance distribution of cases was ensured by giving phenindione to patients admitted on even days of the calendar month; those admitted on odd days formed the controls. Minor additions to and subtractions from the two main series were necessary (see below) but these had no effect on the outcome of the trial.

Clinical Responsibility and Investigation

The patients were under the clinical care of one of six consultant surgeons, and our arrangement with them was to carry out the trial and control phenindione dosage without influencing other therapy.

Soon after admission one of us took a medical history and made a general examination, noting any condition likely to be influenced by phenindione. The hæmoglobin and blood-urea were often estimated soon after admission. The lower limbs were examined three or four times a week to detect the clinical onset of thrombosis, and any pulmonary or cardiovascular disorder was assessed with regard to the possibility of pulmonary embolism. The milestones to recovery—day of operation, sitting out, first days using crutches and on sticks—were recorded.

A diagnosis of clinical thrombosis or embolism was reported to the clinical staff; responsibility for initiating anticoagulant treatment of those in the control series was theirs; but the dosage of phenindione was controlled by us. Ethically the trial was considered justifiable because the patients in the control series were not treated differently from previous practice. Indeed a higher proportion of those with clinical thrombosis received anticoagulant treatment than before the trial.

TABLE II—GENERAL COMPARISON OF THE PATIENTS IN THE PHENINDIONE AND CONTROL SERIES. (NUMERALS REFER TO NUMBERS OF CASES)

Clinical details and state on admission	Phenindione series	Control series
Total no.	150	150
Males/females	23/127	29/121
Age (yr.):		
55–65	19	10
66–75	40	44
76–85	66	74
>85	25	22
Mean	76·8	77·6
Femoral fracture:		
Pertroch./subcap.	61/89	83/67
R/L	68/82	71/79
General health:		
Good	77	74
Fair	59	51
Poor	14	25
Nutrition:		
Obese	36	28
Average	93	94
Thin	21	28
Ambulant before injury:		
+	128	138
±	15	6
0	7	6
Mental state:		
Good	113	99
Moderate	17	28
Poor or senile	20	23
Hypertension (mm. Hg):		
Systolic 160–200	57	51
Systolic >200	21	25
Congestive cardiac failure:		
Slight	7	5
Definite	5	12
Hemiplegia	4	6
Blood-urea >60 mg. per 100 ml.	6/52	9/52
Anæmia (Hb <10 g. per 100 ml.)	11/139	10/142
Chronic bronchitis and/or emphysema	15	12
Carcinoma	8	2
Diabetes	2	0
Epilepsy	2	2
Colostomy	1	1
Ulcerative colitis	0	1
Diverticulitis	0	2
Peptic ulcer (recently active or active)	0	0
Arthritis	29	30
Varicose veins	16	12
Previous venous thrombosis	6	0
Previous fractured femur	2	4
Amputated leg	2	0
Jaundice	1	0
Parkinson's syndrome	1	1

TABLE III—OPERATION AND DAY OF OPERATION. (NUMERALS REFER TO NUMBER OF CASES)

Pinning or nailing operation	Phenindione series	Control series
All operated patients	142	125
Operated:		
Day of admission	11	10
Next day	60	53
2 days after admission	22	15
3–4 ,, ,,	38	33
5–7 ,, ,,	6	9
>7 ,, ,,	5	5
Operated:		
Day of injury	4	6
Next day	48	37
2 days after injury	30	21
3–4 ,, ,,	39	32
5–7 ,, ,,	10	17
>7 ,, ,,	11	12
Patients not operated on	8	25

Phenindione Series

This comprised 150 cases. Phenindione was administered to the first 21 patients from the day after the hip operation, because of the fear of hæmorrhage. Confidence was gained after three months, and phenindione was then given on the day of admission or the following morning and generally before operation. Surgery was often carried out at effectively lowered plasma-prothrombin levels. The drug was continued during the period of bed rest and training to ambulation until the patient was making satisfactory progress on sticks or crutches. The period of prophylaxis depended on the progress to ambulation; it ranged from 2 to 12 weeks but was usually 3 to 6 weeks and the mean period was 5 weeks. Therapy was continued in 21 patients after discharge, usually for a few days up to 3 weeks, but in 2 cases for a further 4 and 10 weeks. Phenindione was contraindicated in 15 cases (phenindione-reject group) and 8 other cases were excluded from the phenindione series (see below). These 23 cases mainly accounted for the controls outnumbering the phenindione series throughout most of the trial (table I). To balance the numbers 8 unselected cases admitted on odd days during two periods of the trial (in April, 1958, and in February, 1959) were given phenindione prophylaxis.

Dosage of Phenindione and its Control

Usually an initial dose of 200 mg. of phenindione was given followed next day by 100 mg. and then 25, 50, or 75 mg. daily. The details varied, but small amounts of drug generally sufficed to maintain an effectively low plasma-prothrombin level in these elderly subjects. Small doses (25 mg.) often sufficed in the few days following operation, whilst rather larger dosage (50–100 mg.) was necessary in convalescence. When a patient became systemically ill smaller dosage generally sufficed, and on some days the drug could be omitted.

Dosage was controlled by the one-stage plasma-prothrombin estimation of Quick, daily for the first 3 days and then two or three times a week while the patients were in hospital. Special attention was paid to regular estimations to maintain effective drug activity. When necessary, weekly blood samples were collected after discharge either when the patient re-attended hospital as an outpatient or by the patient's own doctor. The

aim of dosage was to prolong the prothrombin-time of the patient's plasma to between two and three times that of normal persons, corresponding on our calibration chart to between 30% and 15% of normal prothrombin activity. With the thromboplastin used, normal plasmas gave a prothrombin-time of 12 to 14 seconds; so dosage was increased or decreased when it fell outside the limits of about 25 to 40 seconds. A saline extract of acetone-dried human brain was the source of thromboplastin; it was made up weekly from the powder. This preparation and the dried material were stored at −20°C when not in use.

The urine and fæces were examined for blood whenever the plasma-prothrombin level fell to undesirable levels, when there was excessive bleeding from the operation wound or elsewhere, and at other times. Urine was routinely examined for blood after transfusion. Salicylates were forbidden because they enhance the effects of phenindione and are likely to produce intestinal bleeding.

TABLE IV—FREQUENCY OF CLINICALLY RECOGNISABLE DEEP-VEIN THROMBOSIS, AND FREQUENCY AND DEGREE OF THROMBOSIS AT NECROPSY

—	Phenindione series	Control series
Total patients	150	150
Clinical venous thrombosis	4*	43
Total deaths	25	42
No. of vein-dissected necropsies:	21	35
With +++ thrombosis	2†	13
With ++ thrombosis	0	12
With + thrombosis	1†	4
With ± thrombosis	5	3
With 0 thrombosis	13	3

* Delayed admission (1); prolonged semiconfinement to bed (1); difficulty in effective phenindione dosage (2 cases).
† Phenindione therapy stopped days or weeks before death and pulmonary embolism present (see table VI).
0, ±, +, ++, and +++ thrombosis: see text.

Phenindione-rejects Group

15 patients admitted on even days of the month were not given phenindione because of a special danger of hæmorrhage. (1 was put on phenindione for a few days, but melæna developed and therapy was stopped.) There were 3 other patients with active bleeding (2 with hæmatemesis, 1 with hæmaturia); 4 patients with symptoms or a recent history of peptic ulceration (1 with a history of bleeding); 3 patients with a recent hemiplegia; 1 case of polycythæmia vera with recent hæmoptyses; 1 case of hæmophilia; 1 patient with very extensive ecchymosis of the injured thigh; and 1 case of bronchiectasis with attacks of hæmoptysis. Advanced age, hypertension, chronic renal failure, jaundice, cystitis, and obesity were not considered contraindications. One case is noteworthy.

A woman of 70 was admitted 2 days after injury on an even day of the month. She had a history and symptoms of a gastric ulcer, and phenindione was not given. Next day she had tremendous melæna with hæmatemesis and was kept alive by a transfusion of 35 pints of blood over a few days; partial gastrectomy was performed on the 9th day. Had phenindione been given it would have been difficult to argue that it was not responsible for the hæmorrhage. This could have undermined confidence in the safety of the drug, to the detriment of the trial. On the 18th day she collapsed and died and, paradoxically, necropsy revealed a large pulmonary embolism.

TABLE V—NUMBERS OF DEATHS AND NECROPSIES, IN HOSPITAL AND AFTER DISCHARGE *

Group	Died in hospital		Died after discharge		All deaths	
	Total	No. necropsies	Total	No. necropsies	Total	No. necropsies
Phenindione:						
Series	18	18	7	3	25	21
Rejects	3	2	2	2	5	4
Control:						
Series	32	30	10	7	42	37
Rejects	2	1	1	1	3	2
Total	55	51	20	13	75	64

* Within three to four months after injury.

TABLE VI—RESULTS: FREQUENCY OF MAJOR AND MINOR PULMONARY EMBOLISM AT NECROPSY

Group	Total cases	No. of deaths	No. of necropsies	No. with major embolism	No. with minor "incidental" embolism	Total with embolism
Phenindione:						
Series	150	25	21	2*	1*	3*
Rejects	15	5	4	2	1	3
Control:						
Series	150	42	37	15	6	21
Rejects	4	3	2	0	0	0

* In patients in whom phenindione therapy had been stopped.
Note.—(1) In 15/42 deaths (36%) in control series there was major pulmonary embolism. (2) 15/150 patients (10%) in control series developed major pulmonary embolism. (3) Most of the excess of deaths in the control series compared with the phenindione series is accounted for by major pulmonary embolism.

Control Series

This also comprised 150 cases. 8 of the patients were admitted on even days of the month; they were early cases excluded from the phenindione series because operation was decided against (3 cases) or delayed for from 4 to 15 days after admission (5 cases) and policy at the time was to begin phenindione postoperatively but not late. 4 of them died—2 non-operation and 2 late-operation cases, 1 of the latter from pulmonary embolism and the other 3 from hypertensive cardiac failure (2) and coronary-artery disease. One of the late-operation cases developed clinical thrombosis and was treated with anticoagulants. The overall fatality-rate and the frequencies of fatal embolism and clinical thrombosis in the control series (table x) were only slightly influenced by these additions.

TABLE VII—TYPE OF EMBOLISM FOUND AT NECROPSY RELATED TO THE MODE OF DEATH. (NUMERALS REFER TO NUMBERS OF CASES)

Mode of death	Pulmonary embolism at necropsy		
	Bifurcation type or large emboli at both hilar	Large emboli in one or more major branches	Multiple small emboli
Sudden	6	3	1*
Gradual deterioration	2	3	1
Acute congestive failure	1	..	1
Acute hypotension and renal failure	..	1	..

* In bifurcation of pulmonary artery as well as in peripheral branches.

16 of the control series in whom clinical thrombosis developed and 1 with pulmonary embolism were treated with phenindione.

Control-rejects Group

4 patients admitted on odd days of the month were given phenindione for reasons other than clinical thrombosis or embolism: 1 for senile gangrene of the toes (phenindione from day 4 to 14 after injury), 1 for suspected coronary thrombosis (phenindione from day 10 to 49), and 2 because operations had

TABLE VIII—PHENINDIONE SERIES: THROMBOSIS AT NECROPSY RELATED TO (1) DELAY BEFORE STARTING PHENINDIONE THERAPY, AND (2) INTERVAL BETWEEN END OF PHENINDIONE ACTIVITY AND DEATH

Days between end of phenindione activity and death	Days between injury and start of phenindone					
	1	2	3	4	5	10
0	0, 0, 0, 0	0, 0, 0	±	0, ±	0, ±	..
1	0	0	..	±	..	..
2	..	..	0	..	..	..
3	..	..	..	..	..	..
4	..	..	..	..	+	0
9	..	+++	..	..	..	..
12	..	±	..	..	..	..
35	..	+++	..	..	..	..

0, ±, +, ++, and +++ thrombosis are defined in the text.
Each entry is the result in 1 case.

TABLE IX—CAUSES OF DEATH

Main cause	Pulmonary embolism			Bronchopneumonia			Hypertension			Coronary-artery disease	Carcinoma	Enlarged prostate and complications	Other causes	Total deaths	Total cases
Subsidiary cause(s)	Alone	Pneumonia	Total	Alone	Cardiac disease§	Total	Cardiac failure and pneumonia	Coronary sclerosis or cerebral infarct	Total						
Phenindione:															
Series.. ..	2*	0	2	13†	1	14	2	1	3	2	3	1	0	25	150
Rejects ..	1	1	2	2	0	2	0	1	1	0	0	0	0	5	15
Control:															
Series.. ..	11	4	15	12‡	3	15	5	1	6	2	0	1	3	42	150
Rejects ..	0	0	0	2	0	2	0	0	0	0	0	1	0	3	4

* After stopping phenindione therapy.
† 1 also Sonne dysentery.
‡ 1 also minor cerebral infarction.
§ Hypertensive failure, myocardial fibrosis or congestive cardiac failure.

to be postponed and the surgeons feared embolism (phenindione from day 1 to 39 in one and from day 3 to 27 in the other). Obviously these cases could not be included among the control series.

Diagnosis of Clinical Venous Thrombosis

Reliance was placed on unexplained unilateral swelling of a leg, postoperative swelling of the operated thigh being ignored. Unequivocal spontaneous pain or tenderness in the calf and a definite Homan's sign were also of value, but they were often absent. A sensation of tightness in the calf was sometimes useful as an early sign. The same criteria of diagnosis were applied strictly to all patients so that any diagnostic errors were likely to be equal in the phenindione and control series.

Follow-up

Each survivor was followed up for at least three months from the time of injury. After discharge the major purpose was to ascertain survival and to obtain necropsies. A letter was sent to the patient's doctor requesting immediate notification of death, and attendances at the outpatient and rehabilitation departments were checked. Another letter, if necessary, was sent at the end of the 3-month period to verify that the patient still lived. Every patient was accounted for. Of the 264 patients who were discharged from hospital 20 died and 13 were examined post mortem (table v). 5 of the necropsies were done by other pathologists, but one of us fully dissected the lower-limb veins and pulmonary arteries in 2 of them, and in 2 other cases (with pulmonary embolism) the veins were partly dissected.

TABLE X—SUMMARY OF MAIN RESULTS OF THE TRIAL

Group	Total patients	No. of deaths	Venous thrombosis		Pulmonary embolism		Cases with any thrombo-embolic incident ‡
			Clinical	At necropsy (+, ++, or +++)	Major, causing or contributing to death	Minor, clinical, or pathological	
Phenindione:							
Series ..	150	25	4*	3†/21	2†	1†	7*†
Rejects ..	15	5	0	2/4	2	1	3
Control:							
Series ..	150	42	43	29/35	15	12	59
Rejects ..	4	3	0	1/2	0	0	0

* 1 patient admitted 9 days after injury and bed rest; 1 patient semiconfined to bed for 2 years before accident; in 2 difficulty in establishing phenindione dosage and effective activity.
† Phenindione therapy stopped days or weeks before death.
‡ Excluding silent venous thrombosis found at necropsy.

Venous Dissection at Necropsy

The lower venous tree was examined from the inferior vena cava to the posterior tibial veins at the ankles by slitting the veins with scissors. First, the vena cava and the common, internal, and external iliac veins were opened. The inguinal ligament was then divided and the incision continued distally along Hunter's canal; the common, superficial, and profunda femoral veins were opened, also the upper part of the saphenous vein and as much as possible of the medial and lateral circumflex veins and large intramuscular veins. The body was then turned face downwards; a deep oblique incision cutting the adductor ring was made from the distal end of the anteromedial thigh incision to behind the knee, so exposing the popliteal vein; a midline incision down the back of the leg split the gastrocnemius and soleal muscles longitudinally and exposed the floor of the deep posterior compartment. The popliteal vein and the posterior tibial veins were then opened. The intramuscular veins of the soleal and gastrocnemius muscles were examined for thrombi mainly by deep transverse cuts.

Vein dissections were carried out in 35 of the control series (42 deaths), in 21 of the phenindione series (25 deaths), in 4 of the phenindione-reject cases (5 deaths), and in 2 of the control-reject cases (3 deaths).

Comparison of Phenindione and Control Series

The anticipation that the phenindione and control series would be similar was justified (table II). Females predominated, forming 84% of the phenindione series and 81% of the controls. The mean ages were 76·8 and 77·6 years respectively, whilst 61% of the phenindione series and 64% of the controls were over 75 years of age. There was some excess of cases in the 55–65-year group of the phenindione series and in the 76–85-year group of the controls. Other differences which were mainly related to the difference in age-distribution were: 9% of patients in poor general health in the phenindione series, compared with 16·6% of the controls; 3% with definite congestive cardiac failure in the phenindione series, compared with 8% of the controls. There was also a difference in the frequency of pertrochanteric and subcapital fractures: 41% had pertrochanteric fractures in the phenindione series and 55% in the controls. Otherwise the groups are closely similar.

The outcome of the trial was not affected by these differences or by the excess of non-operated cases in the control series because the prophylactic effect of phenindione was so clear-cut. Table III shows that the numbers operated on on the day of admission or injury and on subsequent days were similar in both series; the only significant difference was a greater number of non-operated cases in the control series (25 cases) compared with the phenindione series (8 cases). A decision not to operate was usually made on medical grounds, so the excess of non-operated cases is related to the difference noted above in age and health and to excess of non-embolic deaths in the control series (table IX). The higher fatality-rate of non-operated controls (36%) compared with those operated on (26%) is not surprising.

TABLE XI—MAJOR EMBOLIC COMPLICATIONS RELATED TO CLINICAL THROMBOSIS

Group	Cases of clinical venous thrombosis	Major pulmonary embolism	
		With clinical thrombosis	Without clinical thrombosis
Phenindione:			
Series..	4	0	2
Rejects	0	0	2
Control:			
Series..	43	8	7
Rejects	0	0	0
Total	47	8	11

Results

CLINICAL

Prevention of Clinical Thrombosis

There were 43 cases of clinically diagnosable thrombosis in the control series (28·7%), compared with only 4 cases in the phenindione series (2·7%)—a reduction of over 90% in frequency (table IV).

In 2 of the 4 failures thrombosis was probably already present before admission, although leg swelling appeared only after sitting out of bed or using a walking machine. Of these 2 patients 1 was admitted 9 days after the fracture and had been in bed all that time. The other had been semiconfined to bed for 2 years, had severe varicose veins, and gave a history of recurrent phlebitis; the leg of the injured limb was slightly swollen on admission. In the 2 other cases larger dosage was needed than is usual in elderly patients; the plasma-prothrombin levels were ineffectively lowered from the 7th to 12th day in 1 case and during the first 4 or 5 days in the other. Leg swelling then appeared and lasted 4 and 11 days respectively. The 4 patients survived and none developed embolism.

These cases illustrate that thrombosis may sometimes develop before admission or even before injury and that early institution of effective dosage is needed for full protection.

Shortening of Inpatient Stay

In the control series the average inpatient stay of the survivors with clinical thrombosis was 54·2 days. This is 15 days longer than the mean stay of control survivors without clinical thrombosis (39·2 days) and about 12 days longer than the mean inpatient stay among survivors in the phenindione series (42·4 days). Thus prophylaxis with phenindione should save bed time, reduce the cost per inpatient, and increase the turnover of patients by preventing clinical thrombosis.

Prevention of Non-fatal Embolism

8 of the controls had non-fatal attacks of pulmonary infarction or embolism. 2 were treated with phenindione and all recovered. In 2 others recovery after an embolic attack was followed by fatal embolism. No case in the phenindione series developed non-fatal clinical embolism.

DEATHS AND NECROPSIES

Special efforts were made to obtain necropsies to discover all cases of embolism and to find out whether thrombi had really been prevented in those given phenindione. This is the most important part of the evidence.

Fatal Pulmonary Embolism

Reliance on the classical clinical criteria underestimates the incidence of fatal embolism. In the present series only about half of the cases of fatal embolism collapsed and died within minutes or hours (table VII). The manner of death varies and can also be gradual deterioration, acute onset of congestive cardiac failure, or a sudden attack of hypotension possibly resulting in acute renal failure (see Sevitt 1959). Necropsy evidence is more reliable; unfortunately a 100% necropsy-rate was not achieved but 21 of the 25 deaths (84%) in the phenindione series and 37 of the 42 deaths (88%) among the controls came to necropsy (table V).

Major embolism is classified as either: (1) a long embolus usually coiled or twisted, straddling the bifurcation of the pulmonary artery or large emboli blocking both main pulmonary arteries at the hila of the lungs; (2) one or more large emboli in major pulmonary arteries; or (3) *multiple* small or medium calibre emboli scattered in the central and peripheral branches of the pulmonary arteries.

Fig. 1—Common and deep femoral veins: venous thrombosis absent except for small thrombus confined to valve-cusp at junction of common and deep femoral veins (patient given phenindione prophylaxis).

Major embolism was found in 15 of the control series, in 2 of the phenindione-reject cases, and in 2 of the phenindione series (table VI). Thus 36% of the deaths and 10% of the cases in the control series had embolism judged to have been either the sole or a major contributory cause of death. The emboli found are related to the modes of death in table VII.

The onset of embolism was dated in 13 of the 19 cases from the history and nature of the emboli. 1 case occurred on the 6th day after injury; 3 cases between the 12th and 14th days; 4 between the 17th and 19th days; and single cases 25, 27, 44, 57, and 69 days after injury. The other 6 patients died, after gradual deterioration, on the 17th, 28th, 33rd, 35th, 38th, and 120th days after injury.

The 2 deaths from embolism in the phenindione series occurred after therapy had stopped, so they were not really failures of current prophylaxis. Indeed no patient developed embolism whilst under the influence of phenindione. There is no difficulty in stopping phenindione in patients who achieve mobility and are active, but these 2 cases raise the problem of when it is safe to stop the anticoagulant in elderly inactive patients of whom some may never achieve proper mobility and others, after discharge as reasonably mobile, spend much or most of their day in bed through the misguided kindness of their family or attendants. Both cases are instructive.

A woman of 87 was maintained on phenindione from the 2nd to the 60th day after injury and was then discharged reasonably mobile to a nursing-home. She was put to bed there and died 35 days later. Necropsy revealed major pulmonary emboli at the hila of both lungs, and lung infarction; gross and extensive thrombosis of thigh and leg veins was present.

In the other patient (a woman of 80) phenindione was discontinued on the 18th day after injury as she was reasonably mobile on a walking frame. 4 days later she collapsed and died within a few minutes; necropsy showed multiple thin emboli

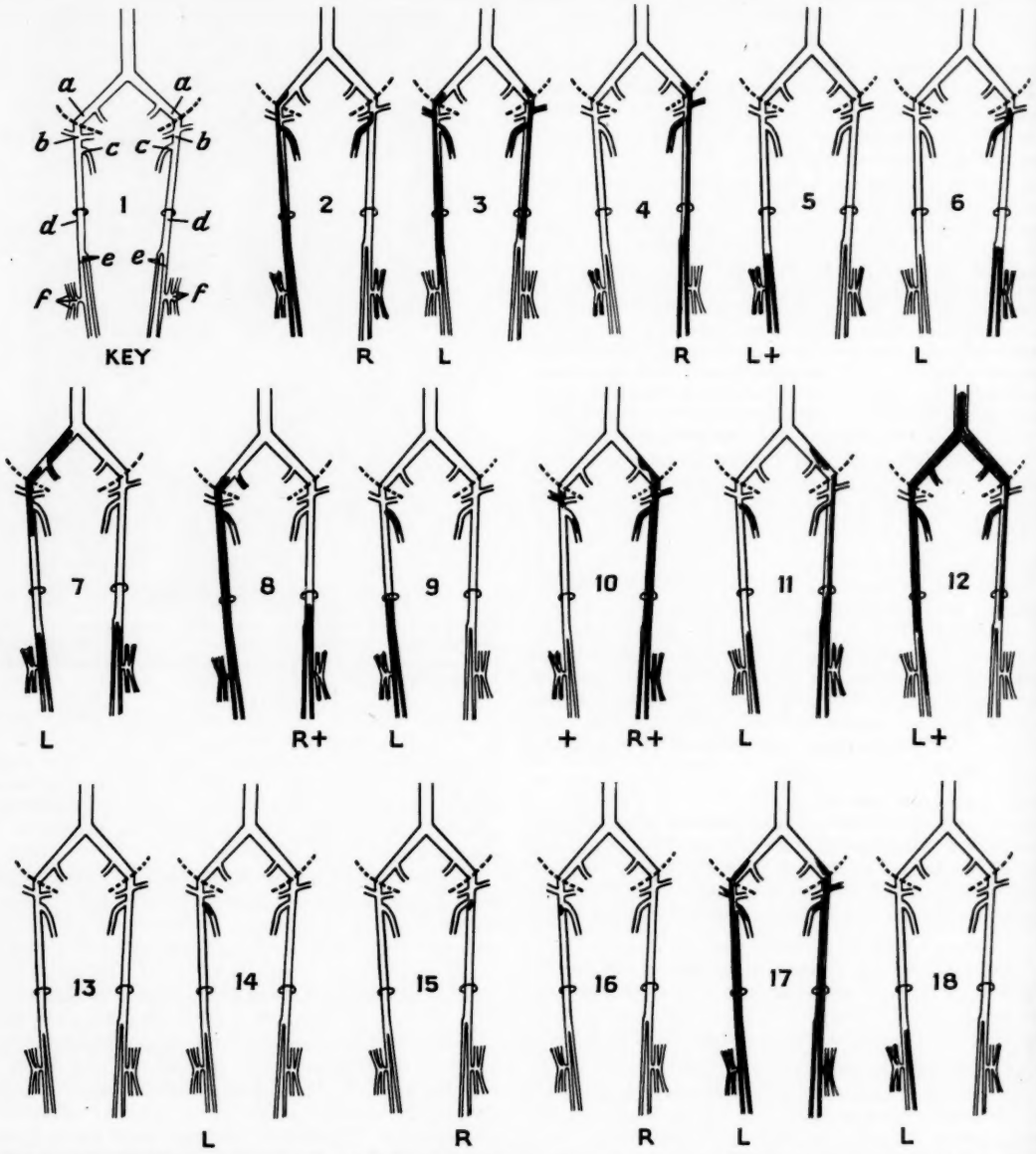

Fig. 2—Deep-vein thrombosis at necropsy (R or L indicates side of fracture; +, the presence of clinical venous thrombosis). 1 shows the six primary and independent sites of deep-vein thrombosis in the lower venous tree (see Sevitt 1959): a, external iliac; b, common femoral; c, profunda femoral; d, popliteal; e, posterior tibials; f, soleal. 2–6 are illustrative cases from the control series without pulmonary embolism; 7–12 are illustrative cases from the control series with major pulmonary embolism at necropsy; 13–18 illustrate the results in the phenindione series.

Case 2.—F, 84 years, died 8 days after R pertrochanteric fracture.

Case 3.—F, 76 years, died 10 days after L pertrochanteric fracture.

Case 4.—F, 79 years, died 19 days after R subcapital fracture.

Case 5.—F, 80 years, died 28 days after L subcapital fracture.

Case 6.—M, 78 years, died 59 days after L subcapital fracture.

Case 7.—F, 85 years, died suddenly 6 days after L subcapital fracture.

Case 8.—F, 75 years, died suddenly 14 days after R subcapital fracture.

Case 9.—M, 80 years, died suddenly 13 days after L subcapital fracture.

Case 10.—F, 78 years, died 21 days after R pertrochanteric fracture; acute hypotension from 19th day.

Case 11.—M, 72 years, died 23 days after L pertrochanteric fracture; acute congestive cardiac failure from 14th day after injury.

Case 12.—F, 84 years, died 4 months after subcapital fracture, L femur; gradual deterioration.

Case 13 illustrates absence of any thrombosis in 13 of the 21 necropsies among the phenindione series.

Cases 14–16 illustrate minimal (±) thrombosis in femoral or soleal veins in 5 cases of the phenindione series (fig. 1). This usually antedated phenindione prophylaxis.

Cases 17 and 18.—2 of the 3 cases in the phenindione series found to have extensive or significant thrombosis at necropsy. In case 17 phenindione was discontinued 9 days before death; and in case 18 4 days before death. Case 18 died of pulmonary embolism.

coiled at the bifurcation of the pulmonary artery and also in main and central branches in both lungs; thrombi were present in posterior tibial and soleal veins (fig. 2, case 18). The patient had been transferred to another ward on the 18th day in preparation for discharge from hospital, but had been allowed to become inactive and sit in a chair most of the day.

Minor Pulmonary Embolism

A few small emboli in central or peripheral branches of the pulmonary arteries were found in 6 cases of the control series and in 1 of the phenindione series (table VI). This minor or incidental embolism is not considered of clinical significance, but its absence also demonstrates the protective action of phenindione.

The case in the phenindione series was in a patient who died 9 days after discharge from hospital; phenindione had been given until discharge on the 24th day after injury. Extensive, soft, recent thrombosis was present in the veins of both thighs and legs (fig. 2, case 17).

No patient developed even incidental embolism whilst under current administration of phenindione.

Deep-vein Thrombosis at Necropsy

The extent of thrombosis may be defined as 0, no thrombosis; ±, small thrombi in a valve cusp of a femoral vein (fig. 1) with or without very small thrombi in soleal or posterior tibial veins (this degree of thrombosis is very minor and involves no hazard of significant embolism); +, significant thrombosis confined to the veins of the legs; ++, thrombosis in leg and thigh veins of one or both limbs capable of causing major embolism from thigh-vein thrombosis; and +++, extensive, continuous thrombosis in veins of one or both legs and thighs.

Thrombosis was very common and extensive in the control series and absent or slight in the phenindione series except in 3 special cases (table IV and fig. 2). Significant or extensive thrombosis (+, ++, or +++) was found in 29 of the 35 necropsies in the control series (83%), compared with 3 of the 21 in the phenindione series (14%): expressed differently, thrombosis was absent or insignificant (0 or ±) in 86% of the phenindione series and in 17% of the control cases. The 3 cases with + or +++ thrombosis in the phenindione series were those with major or minor embolism at necropsy, in which phenindione had been discontinued days or weeks before death. Thus no patient developed significant deep-vein thrombosis whilst under the influence of phenindione.

There is evidence that even the minor thrombosis (±) (fig. 1) occurred before anticoagulant therapy had started or, in 1 case, after it had been stopped. In table VIII thrombosis at necropsy is related (1) to the interval between injury and the beginning of prophylaxis, and (2) to the period between the end of phenindione activity and death. Thrombosis was completely absent in the 9 patients in whom therapy was begun within 2 days of injury and who died during anticoagulant prophylaxis or within a day or two of its being stopped. Thrombosis was minor and insignificant (±) in 4 of the 7 cases in which therapy had been delayed for 3 to 5 days after injury and was absent in the other 3. Histological section of 2 of these thrombi showed the presence of hæmosiderin confirming that they were not freshly formed. They were probably laid down before the anticoagulant was given. The other patient with minor thrombosis died 12 days after phenindione had been discontinued and is thus amply explained; hæmosiderin was absent histologically.

The evidence indicates that phenindione prevents venous thrombosis but emphasises that therapy should be begun within 2 or 3 days of injury and should be continued until there is no further danger of thrombosis.

Causes of Death

Table IX gives the numbers of deaths from different causes. There were 42 deaths in the control series (fatality-rate 28%) and 25 in the phenindione series (17%)—an excess of 17 cases (11%). Most of the difference is accounted for by the 13 extra cases of fatal embolism in the control series. The reduction in deaths from pulmonary embolism was not associated with an increase in the number of deaths from bronchopneumonia or other causes; on the contrary there was almost the same number of deaths from bronchopneumonia in both series (14 and 15 cases). It can be concluded that prophylaxis with phenindione not only prevents deaths from pulmonary embolism but also saves at least a corresponding number of lives.

The number of non-embolic deaths in the control series (27) is rather greater than the number among the phenindione series (23). The few extra deaths from hypertensive cardiac failure among the controls account for this and are consistent with the excess of control cases in the 76–85-year age-group, the larger number of non-operated cases, and those admitted in poor general health and congestive cardiac failure (tables II and III).

SAFETY OF PHENINDIONE

Operative Bleeding

The surgeons reported that the wounds of patients under phenindione bled no more than the controls during the hip operations. This is supported by comparing in the two series the volumes of blood transfused during and immediately after operation. Since the Smith-Petersen pinning (for subcapital fractures) is a less bloody operation than the Neufeldt nail-plate procedure, each series was divided according to which operation was used.

Comparison of the transfusion volumes administered to those subjected to Smith-Petersen pinning (53 controls, 20 given phenindione after operation, 58 given phenindione before operation) showed that no extra blood was given to the phenindione-treated. In about half the operations in each subgroup transfusion was not given, and when it was 1–2 pints was nearly always transfused. Analysis of the phenindione series according to plasma-prothrombin levels on the day of operation (16 cases, 10–30% of normal activity; 18 cases, 30–60%) showed that no extra blood was given at any therapeutic level of plasma-prothrombin activity.

Comparison of the volumes of blood transfused in patients having Neufeldt nail-plate operations (69 controls, 23 given phenindione postoperatively, 41 given phenindione before operation) showed that half to three-quarters of them were transfused with 1 to 3 pints, but the scatter was greater than in those having the Smith-Petersen operation. The number of cases with effectively lowered plasma-prothrombin levels on the day of operation (11 patients, 10–30% of normal activity; 13 cases, 30–60%) was too small for definite conclusions to be drawn. At worst it can be said that if extra blood was given to some the amount was no greater than 1 pint.

Postoperative Hæmorrhagic Complications

These are classified into: (1) minor incidents not requiring special treatment, and (2) major incidents needing surgical intervention, blood-transfusion, stopping phenindione therapy, or reversal of drug action with vitamin K_1. There was an excess of minor incidents among the phenindione series (30 cases or 20%) compared

with the controls (12 cases, 8%), but most of the difference is due to cases of minor wound hæmatomata and postoperative oozing controllable by a simple pressure bandage. There were also a few more cases with minor epistaxis, microscopic hæmaturia, or occult blood in the fæces in the phenindione series (total of 8 cases) than in the controls (total 3 cases). The degree of bleeding was of no clinical importance. Minor bleeding is an inevitable accompaniment of effective therapy in some cases (Toohey 1957) and indeed is an index of the effectiveness of phenindione in the group as a whole.

Major incidents were few: 2 cases among the controls (1 wound hæmatoma requiring surgery and 1 case of postoperative bleeding needing transfusion) and 5 among the phenindione series. At least 1 and at most 3 of these 5 can be attributed to phenindione: 1 case of postoperative hæmorrhage needing a transfusion of 3 pints of blood (plasma-prothrombin 11% of normal) and possibly cases of a small melæna and a small hæmatemesis. The other 2 cases—a wound hæmatoma and bleeding from a fungating breast cancer—were considered ordinary surgical complications.

Discussion

It has been shown that phenindione given prophylactically and in effective dosage prevents thrombosis in veins and eliminates the risk of pulmonary embolism. This answers the criticisms made by various workers (e.g., Blake et al. 1959) that there is no direct evidence that anticoagulants with coumarin or coumarin-like activity prevent thrombosis. For maximum protection phenindione must be started soon after the patient is put to bed after injury, and its effect must be maintained until the state of mobility is able to prevent venous stasis and eliminate the danger of thrombosis. Reduction of the plasma " prothrombin-activity " to between 15% and 30% of normal effectively prevents thrombosis, and daily phenindione dosage sufficient to achieve this is without danger. Possibly a lesser reduction of prothrombin-activity may achieve the same result, but this was not investigated. Phenindione therapy is safe, unless it is specially contraindicated (see below); pinning and nailing operations on the hip can be carried out without fear or danger of excessive bleeding, while hæmorrhagic complications of clinical significance are very few.

The main results of our controlled clinical trial are summarised in table x. Clinical venous thrombosis developed in 43 of the 150 subjects in the control series (28·7%) compared with only 4 of the 150 patients given phenindione (2·7%), whilst even these 4 may have resulted from thrombosis before admission to hospital or difficulty in establishing or maintaining effective phenindione dosage. Even more conclusive is a comparison of the necropsy frequency of thrombosis in the deep veins of the lower limbs; significant or extensive thrombosis was found in 29 of the 35 controls studied (83%) compared with only 3 of the 21 of the phenindione series examined (14%). These 3 died after cessation of prophylaxis, so they were not failures of current therapy. The whole lower venous tree was completely free of thrombi in most cases examined post mortem in the phenindione series; in some, very minor thrombosis was found but this usually antedated and occasionally postdated prophylaxis.

The prevention of thrombosis was reflected in the prevention of embolism. No case of embolism occurred in patients under the influence of phenindione, compared with 15 cases (10%) of fatal embolism and a total of 27 cases (18%) of all degrees of pathological and clinical embolism among the controls. The 2 cases of fatal embolism and the 1 of incidental embolism among the phenindione series were in patients who died after therapy had been stopped; they were the ones also found to have thrombi in veins. These cases indicate the sometimes difficult problem of when it is safe to stop the drug in elderly inactive patients.

Excluding the deep-vein thrombosis revealed at necropsy, almost 40% of the control series developed some form of thromboembolic incident compared with 4·7% of the phenindione series—and the latter can be explained.

The reduction of fatal embolism was associated with a lowered fatality-rate; there were 25 deaths in the phenindione series (16·6%) and 42 deaths among the controls (28%), and most of the excess of deaths is accounted for by the cases of fatal embolism. This surely means that prophylactic phenindione not only prevented deaths from embolism but saved a corresponding number of lives.

Two questions arise. How many of the control series would have died from embolism, first, if *none* of the patients developing clinical thrombosis had been treated with phenindione, and second, if *all* those with clinical thrombosis had been so treated? The question of prophylaxis versus treatment hangs on the answer to the second question. Table xi shows that 8 deaths from embolism in the control series followed clinical thrombosis whilst the other 7 were unheralded. Of the former group 1 was among 16 cases of clinical thrombosis treated with phenindione (fatality, 6·2%) and the other 7 were among 27 untreated cases (fatality, 25·9%). Assuming these figures apply to all the cases of clinical thrombosis, there would have been 18 cases of fatal embolism (12%) had none of the clinical cases of thrombosis been treated, and 9–10 cases of fatal embolism (6–6·6%) had all the cases of clinical thrombosis been treated with anticoagulants. The latter is a conservative estimate because 1 of the cases with fatal embolism developed clinical thrombosis only a few hours before death—probably too late for effective therapy. Treatment of diagnosed cases of clinical thrombosis could have only halved the incidence of fatal embolism. Half the cases would have still occurred; they form the basis of the superiority of prophylaxis over treatment.

Recommendations

The implications of our trial lie beyond the narrow group of elderly patients with fractured hips. Further work is necessary to strike the balance between the indiscriminate administration of phenindione to every patient admitted with an injury and its restriction to narrow selected groups.

It is reasonable to advocate prophylactic protection at least for those particularly at risk of embolism—that is, those over 50 years of age who are about to undergo a period of bed rest for longer than 2 or 3 days and in whom anticoagulant therapy is not otherwise contraindicated. This would include all middle-aged and elderly patients with a fractured femur or tibia, possibly most of those with a fractured pelvis, as well as those put to bed with bruises and lacerations and possibly restricted burns. This policy should reduce the incidence of fatal embolism in the Birmingham Accident Hospital by 80–90%. Therapy should begin as soon as possible after injury and should be continued until at least 1 week after the patient has

begun to be reasonably mobile and ambulant, if necessary by domiciliary arrangement after discharge from hospital.

Major contraindications to anticoagulant drugs are recent melæna, hæmatemesis or hæmoptysis, peptic ulceration, and hæmorrhagic diathesis. The importance of a careful history and clinical examination cannot be over-emphasised, whilst the possibility of acute duodenal ulceration following trauma has to be borne in mind. Chronic renal or hepatic disease is not considered a contraindication; but less drug, more care, and more frequent prothrombin estimations are often needed.

Contraindications to any prophylaxis must be distinguished from contraindications to early prophylaxis. Early prophylaxis might be dangerous: (1) to patients with cerebral contusion or spinal injury, because of the special dangers of a small amount of additional bleeding; and (2) to patients with severe thoracic or abdominal injuries, because of the risk of major hæmorrhage. There may well be a place for *delayed* prophylaxis in these patients—that is, to begin phenindione several days after injury at a time when the early dangers of hæmorrhage have passed. This problem will have to be solved through further experience. It must not be assumed that the freedom from undue hæmorrhage which we have found with nailing and pinning operations on the hip applies to all surgery; on the other hand it is likely that many operations can be carried out quite safely. Toohey (1957) states that even major gastrointestinal surgery can be carried out safely in patients continuing to have anticoagulant drugs. Dosage may have to be temporarily reduced.

Anticoagulant Unit

Large numbers of cases for prophylaxis give rise to a need for a properly organised anticoagulant unit in the hospital laboratory. The repeating of plasma-prothrombin estimations over weeks or months can alone add a considerable new load to a laboratory when hundreds of cases have to be dealt with every year. Unfortunately many hospital laboratories are still staffed and housed inadequately in relation to the expansion of the laboratory service, so effective anticoagulant units may not be always possible unless special efforts are made by those in authority to provide the extra needs. This problem has already arisen in relation to the long-term domiciliary treatment of coronary thrombosis with anticoagulants. Phenindione is a cheap drug, so the price of removing the burden of thrombosis and embolism from the accident wards is little more than the cost of an adequately run anticoagulant unit. For those financially minded it should be pointed out that phenindione prophylaxis almost abolishes clinical thrombosis and consequently reduces inpatient stay and cost per patient; this should balance and perhaps outweigh the charge for the extra laboratory facilities.

An anticoagulant unit provides the opportunity of concentrating the control and experience of therapy into the hands of one or two members of the medical staff, usually the hospital pathologist or occasionally a specially interested physician. Central control is preferable to the variable standards of dosage inseparable from peripheral control by different surgeons, or more usually their junior staff.

Summary

A controlled clinical trial is described among elderly patients with fractured hips, of whom 150 were given phenindione (phenindione series) and 150 were not (control series). The patients were otherwise comparable.

Phenindione therapy was begun soon after admission to hospital and was generally continued until satisfactory mobility was restored. Therapy was controlled by repeated estimations of the plasma-prothrombin time, which was prolonged to between two and three times normal.

Such prophylaxis was found practicable and safe, and the fractures were pinned or nailed without significant hæmorrhage.

Embolism occurred in no patient under the current influence of phenindione; but in the control series embolism developed in 18% of cases and fatal embolism in 10%. The 2 cases of fatal embolism and 1 of minor embolism in the phenindione series occurred after therapy had been stopped.

Clinical venous thrombosis occurred in 28·7% of cases in the control series, compared with 2·7% of cases in the phenindione series.

Significant or extensive thrombosis at necropsy was found in 83% of 35 control cases studied compared with 14% of 21 phenindione cases; these 3 patients died after cessation of prophylaxis. In most of the phenindione series the whole lower venous tree was completely free of thrombi.

The evidence indicates that phenindione effectively prevents thrombosis in veins and eliminates the risk of pulmonary embolism in patients under its influence—provided that the drug is given early, for sufficient time, and under laboratory control.

One of us (S. S.) is a part-time member of the scientific staff of the Medical Research Council. It is a pleasure to acknowledge the many colleagues whose help and cooperation made this trial possible. Mr. W. Gissane, clinical director, and the consultant surgeons of the hospital—Mr. F. G. Badger, Mr. J. H. Hicks, Mr. P. S. London, Mr. H. Proctor, and the late Mr. Ruscoe Clarke—gave us their continued support and allowed us to carry out the trial on their patients. The help of many of the nursing staff, especially Sister M. McGillicuddy, Sister E. M. Ross, and Sister B. Riley, was invaluable. Thanks are due Dr. M. Toohey for helpful advice before the trial began; to Mr. G. Billington, H.M. Coroner for Birmingham, for his sympathetic interest and cooperation; and to fellow-pathologists—Prof. J. Webster, Dr. A. Chaplin, Dr. K. Walton, and Dr. W. Whitelaw—for allowing us to participate in their necropsies. The medical and nursing staff of various other institutions were helpful—in particular the matrons of Hollymoor Hospital, Northfield, and the Good Hope, Haven, and Poplars nursing-homes. Without the help of scores of general practitioners the follow-up could not have been successful; special thanks are owed to them. The Birmingham Regional Hospital Board and the Group 25 Hospital Management Committee provided the finance to transport the bodies to the hospital for necropsy of patients who died after discharge. For photographic assistance our thanks are due to Mr. R. Gill and Mrs. V. Montague-Smith, of the hospital photographic department.

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TREATMENT OF BLEEDING PEPTIC ULCER

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DURING the past 20 years we have been particularly interested in the treatment of severe hæmorrhage from the upper gastrointestinal tract. Our management of these conditions has varied considerably during this time, but, for by far the longest period, we have believed that early operation is the best treatment.

Römcke (1938) concluded that a bleeding ulcer should be treated medically. Only when the site of the ulcer was known and when, despite transfusion, bleeding recurred should operation be contemplated.

Römcke and Evensen (1940) reconsidered the problem, particularly as far as later relapses were concerned. In 29% of their cases bleeding recurred and in nearly half (43%) of these there was still further bleeding. We discussed the question of surgery for recurrent bleeding in the free intervals, but decided against it because at that time the mortality of ordinary gastrectomy was 6·7%.

In 1942, for the first time, we suggested more active surgical treatment when Römcke, at a meeting of the Norwegian Society of Internal Medicine in Oslo, reported 3 cases that had been operated on and pointed to the significance of repeated hæmorrhage after admission to hospital (Römcke 1945). A study of 431 cases of bleeding ulcers showed that 38 had severe repeated hæmorrhage after admission to hospital, and 10 (26%) of these died.

Römcke (1951) discussed the material from the period 1935–50 (1001 cases). The period 1935–41, the " pre-operative " period, was compared with the period 1941–50, the " operative " period. No difference in the mortality-rate in the two periods could be proved, which was mainly attributed to the high mortality in the operated patients over 60 years of age (6 out of 8 patients died). It was agreed, therefore, that we should be reserved about operating on patients over 60. The surgeons maintained that we had probably not followed sufficiently closely our indications for operation: if hæmorrhage continues in a patient over 45 after adequate treatment in hospital, resection should be performed immediately. This view is now held by Avery Jones (1956).

DETAILS OF 1433 CASES OF BLEEDING ULCERS

—	Period 1 Jan. 1, 1935–Sept. 16, 1941	Period 2 Sept. 17, 1941–Dec. 31, 1950	Period 3 Jan. 1, 1951–Dec. 31, 1957
No. of patients	262	593	578
Male	165 (*63%*)	393 (*66·3%*)	392 (*67·8%*)
Female	97 (*37%*)	200 (*33·7%*)	186 (*32·2%*)
Average age (yr.)	47·5	52·2	56·1
Over 60	*21%*	*37·7%*	*44·5%*
Hæmatemesis	125 (*47·7%*)	271 (*45·7%*)	275 (*47·6%*)
Duodenal/gastric ulcer	1·7	1·5	1·5

Preoperative X-ray examinations have been avoided, because in our experience they can be misleading. Several times hæmorrhage was caused not by the ulcer seen radiologically but by a second one. This method, however, involves the risk of operating without finding an ulcer, but we still operate. Liavaag and Brennhovd (1955) have followed up the patients who had these " blind " resections, and in no case was there a second hæmorrhage.

In 1951–57 our indications for operation were followed more strictly. To compare this period with the two previous ones, it has been necessary to review all the case-histories. We have excluded some cases in which a cause of bleeding other than ulcer was later established. We did not include bleeding from a jejunal peptic ulcer, which we consider belongs to another category. Finally, we excluded some cases where re-examination of the case-histories raised doubt as to whether hæmatemesis or melæna had really occurred.

Patients and Results

The cases recorded here were those in which the diagnosis of ulcer was definitely established by X-ray examination or by resection, or was highly probable from the clinical findings. In this way the groups should be comparable as far as this point is concerned, and the accompanying table shows that the three periods are comparable in other respects.

The proportion of patients with hæmatemesis is unchanged from period to period, and this also applies to the sex-distribution and the ratio of duodenal to gastric ulcer. The age-distribution, however, shows a considerable displacement towards the older ages in the last two periods. While the average age in the first period was 47·5 years, it was 52·2 in the second, and 56·1 in the third. Patients above 60 formed 21% in the first period, 32·7% in the second, and 44·5% in the third. Despite this displacement in age, the total mortality in the three periods fell progressively:

Period	*Mortality-rate*
1. Jan. 1, 1935–Sept. 16, 1941	5·3% (14/262)
2. Sept. 17, 1941–Dec. 31, 1950	4·9% (29/593)
3. Jan. 1, 1951–Dec. 31, 1957	4·0% (23/578)

The difference was not statistically significant, however, and was largely due to the decreasing mortality in patients under 60: 4·3% in period 1, 2·5% in period 2, and 0·3% in period 3.

For patients over 60 the total mortality-rate was unchanged at between 9% and 10% because death due to other diseases was much commoner in this age-group, particularly in period 3, when many patients were very old (2 over 90).

If we divide the patients into two groups—those who have not had a recurrence or continued hæmorrhage after admission and those who have had a major or minor hæmorrhage after admission the mortality-rate for the second (or recurrence) group is as follows: period 1 16·6% (9/54); period 2 16·9% (23/136); period 3 6·9% (11/159). The difference in mortality between periods 2 and 3 is here statistically significant.

For patients over 60 with recurrence of hæmorrhage we find a statistically significant decline in the mortality from period 2 (32·6%) to period 3 (14·9%). Moreover, twice as many operations were carried out in period 3 as in period 2.

Not all patients with recurrence or continuation of hæmorrhage had surgical treatment, because we have included in this group all cases in which there was the slightest recurrence or continuation of hæmorrhage. There were also in this group a few patitens who refused operation; and sometimes complications made it impossible to operate.

Operation

When operation is decided upon, the patient must be adequately resuscitated, and blood given continuously during the operation. The best anæsthesia is endotracheal narcosis, which avoids aspiration of regurgitated gastric contents.

After the abdomen is opened, a quick examination will demonstrate a gastric or duodenal ulcer in the great majority of patients. An empty stomach does not exclude gastric hæmorrhage, since many patients with massive bleeding have hyperperistalsis of the stomach. If no ulcer can be found, the intestine is examined to exclude other causes of bleeding, such as tumours or Meckel's diverticulum. Thereafter inspection of the liver and the spleen will exclude portal hypertension.

Mobilisation of the stomach and the duodenum in the usual way will sometimes reveal an ulcer on the posterior wall of the stomach.

Sometimes, however, no ulcer can be demonstrated by inspection or palpation, and then the stomach is opened by splitting the front wall lengthwise, almost for its full extent, and the inside is examined. It may be difficult to find even a macroscopical ulcer. A useful guide can be redness and inflammation of the serosa. Another guide is lymph-nodes along the lesser curvature which, when they appear, are usually at the same level as the ulcer. Even then, a number of cases remain in which no macroscopical ulcer can be found. In 30% of our first 50 cases we found no macroscopical ulcer. In the last series this proportion had fallen to 20%. In our opinion increased experience and systematic work make it possible to find the ulcer in more and more cases.

The group where no macroscopical ulcer is found is particularly interesting. When we performed our first so-called "blind" resections, we doubted whether this course was correct, but we found that after a "blind" resection the bleeding usually ceased.

In 2 of our first 15 cases massive bleeding occurred postoperatively. This hæmorrhage may come from the anastomosis or from the stump of the stomach, and in our opinion the stump is the most probable site. Accordingly we have lately performed a very high resection when no ulcer was to be found, almost a subtotal gastrectomy. And since this procedure has been adopted, we have not seen massive postoperative bleeding. We have also re-examined the patients in whom no ulcer was found, and none have had recurrent hæmorrhages—in striking contrast to the high proportion of recurrent hæmorrhages after conservative treatment. We feel that these observations justify the "blind" resection; and that these bleedings are a manifestation of the ulcer disease, and arise from multiple minor erosions or from an overlooked ulcer.

Findings

A gastric ulcer was found in 65 cases, a duodenal ulcer in 32, and no ulcer in 26. In 2 cases the massive bleeding was due to portal hypertension, in 2 to cancer of the stomach, in 1 to reticulosarcoma of the stomach, and in 1 to neurinoma.

A patient with portal hypertension should not, if possible, be operated on during massive bleeding, and when this condition is suspected X-ray examination may be justified during the bleeding, if the diagnosis cannot be established by clinical and laboratory methods.

Hæmorrhagic diathesis or hiatus hernia were not among the causes of bleeding that led to operation. We operated on a patient who was known to have hiatus hernia, but the bleeding seemed to come from a duodenal ulcer.

Operative Mortality

In period 2 35 out of 136 cases were operated on, and immediate postoperative deaths numbered 10 (28·5%). In period 3, 88 out of 159 cases were operated on and 5 died postoperatively (5·7%).

Results in patients over 60, with recurrent or continuing hæmorrhage were as follows:

	Period 2	*Period 3*
Total	49	67
No. operated on	8	29
Deaths in operated group	6 (75%)	4 (13·7%)

It is valuable to look at the causes of death to see whether mortality could be further reduced. Of the 5 patients who died in period 3, only 4 underwent resection. The mortality-rate for those who had a resection is therefore 4·6%.

The patient who did not have a resection had simultaneous perforation and bleeding, and a simple suture was performed. The patient died from continued hæmorrhage. This treatment was wrong: simultaneous bleeding and perforation are often the result of kissing ulcers, with perforation of the front one and bleeding from the back one, and the right treatment is resection. Such an operation is surgical treatment for the perforation, not for the bleeding, and the prognosis of the hæmorrhage would be no better after operation than after conservative treatment. This death should therefore be blamed on the conservative treatment.

Another patient had repeated massive bleeding for several days. He refused operation until he was nearly dead, and was then operated on because of strong pressure from relatives. Aspiration pneumonia and total collapse of one lung ensued and he died ten days after operation. This disaster emphasises that if surgical treatment is undertaken for bleeding ulcer, it should be done early.

2 patients died from continued hæmorrhage after the operation. In 1 necropsy revealed a gastric ulcer 2 cm. above the anastomosis; and in the other a deep-rooted duodenal ulcer. The gastric ulcer should have been discovered during the operation. The duodenal ulcer was so low down that it is questionable whether resection below it was technically possible.

In the 5th case a total gastrectomy was performed because of a technical error during the operation. The patient died of peritonitis.

Some of these deaths could have been avoided, and we believe that the mortality-rate can be reduced until it approaches the mortality of operation for uncomplicated ulcer—and that is our aim.

Summary

1433 cases of bleeding gastric or duodenal ulcers were treated during three periods: 1935–41, when all were treated conservatively; 1941–50, when a few were operated on; and 1951–57, when all patients over 45 with recurrent or continued severe hæmorrhage were operated on early.

Apart from increasing average age from period to period, the three groups are comparable. Despite this, the mortality-rate is decreased. For patients with recurrent or continued hæmorrhage the total mortality fell from 16·6% and 16·9% in the first and second periods to 6·9% in the third period. For patients over 60 there was a statistically significant fall in the total mortality-rate—from 32·6% to 14·9%. Improved surgical technique may reduce the mortality even further.

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GASTRECTOMY FOR MASSIVE GASTROINTESTINAL HÆMORRHAGE OF UNKNOWN CAUSE

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DOUBT still exists about the place of so-called "blind" gastrectomy or "empiric" gastric resection (Thieme 1954) in the management of patients who are operated on for massive hæmatemesis and in whom an obvious lesion is not found on examination of the stomach or duodenum. The weight of surgical experience appears to favour the procedure; but, because the situation is not common, the opinion of any one surgeon is usually based on only a few personal cases. It seemed of value, therefore, to gather together the examples of "blind" gastrectomy in two surgical units where this policy was followed, in order to analyse the results and to compare them with the findings of others. This report deals with 31 cases that were treated in the professorial surgical units of the Edinburgh Royal Infirmary and the Western General Hospital, or in private surgical practice over the past ten years, during which approximately 180 gastric resections for massive hæmorrhage were carried out—an incidence of "blind" gastrectomy of 17%.

Findings

Definition

"Blind" gastrectomy is defined as a standard two-thirds to three-quarters gastrectomy carried out on account of massive hæmorrhage when an obvious lesion is not present on external examination or on palpation of the stomach and duodenum. In this paper, for the purposes of analysis, patients are included who, under such circumstances, were subjected to preliminary gastrotomy, with or without identification of the bleeding-point by this means.

Clinical Features

The cases are summarised in the accompanying table. There were 19 men and 12 women; only 3 patients were less than 40 years of age. The indications for surgical treatment were those usually adopted: massive, often repeated, bleeding in middle-aged or elderly patients with failure of response to blood-transfusion, and absence of any clinical evidence of portal hypertension. Nearly all were admitted under the initial care of a physician or under the combined care of a physician and surgeon.

About half presented either without history of indigestion or with only a few days of vague abdominal discomfort. However, in 4 patients with longer histories, peptic ulcers in either the stomach or the duodenum had previously been demonstrated radiologically, although external evidence of ulceration could not be found at laparotomy. Of the patients with past complaints, 9 had had dyspepsia and 4 actual epigastric pain. Despite the known incidence of massive hæmorrhage in relation to the use of insoluble aspirin (Hurst 1943, Kelly 1950, Muir and Cossar 1955, Lange 1957, Alvarez and Summerskill 1958), in only 3 patients (cases 4, 5, and 13) was excessive intake of this drug an obvious factor in the precipitation of the hæmorrhage. One had taken the drug for chest pain which was subsequently shown to have been caused by an anterior myocardial infarct. Gastrectomy was undertaken in the face of this evidence because of continued bleeding and, with skilled anæsthesia, the patient survived. Ulcers on the lesser curvature were found in the operative specimens of all 3 patients who gave a history of aspirin ingestion. Apart from the sex-distribution there was no definite feature in the history or physical findings which allowed the indentification of the group of indeterminate bleeders preoperatively; but 7 patients were obese—an unusual finding in peptic ulceration in this country.

Operative Findings

In all the cases there was no obvious evidence of active peptic ulceration at laparotomy. In 6 instances the surgeon considered that there might possibly be a healed ulcer, but pathological confirmation in the resected specimen was obtained only once. Despite this low prevalence of identifiable lesions, superficial gastric ulcers or gastric erosions thought to be the cause of the hæmorrhage were found in 19 specimens and a duodenal ulcer in 2. In another patient histological examination suggested that the line of section had passed through a lesser-curve ulcer, and in case 17 an unresected ulcer was found in the duodenal stump. 2 patients had large hiatus herniæ; in 1 (case 6) the resected specimen contained a superficial gastric ulcer, but in the other (case 24) a cause of bleeding was not found. It must be assumed that this patient had either a superficial erosion of the œsophagus or a longitudinal fissure of the Mallory-Weiss type at the cardio-œsophageal junction. He survived operation and œsophagoscopic confirmation was not sought.

Gastrotomy was carried out only once and revealed a superficial gastric ulcer.

Operative Delay

In 7 cases only was operation carried out within twenty-four hours of admission; in 9 the delay was up to two days, and in 15 two to ten days. This presumably reflects the natural unwillingness of both physician and surgeon to submit a patient to operation without good evidence of the cause of the bleeding. In 1 instance (case 11) prolonged delay was almost certainly responsible for the patient's death from hypoxic intestinal dysfunction (case 4 of Dudley et al. 1958). A similar tendency to defer operation has been noted in the published reports of others and may have a bearing on the results.

Mortality and Morbidity

There were 3 deaths.

That of case 11 from intractable paralytic ileus has already been mentioned.

Case 17 succumbed to repeated hæmorrhage from a small anterior ulcer in the duodenal stump which had not been detected at the gastrectomy. This fatality could almost certainly have been avoided if duodenotomy had been carried after the resected specimen had been examined.

The 3rd death (case 25) was from pulmonary embolus in a patient of 74 in whom the immediate postoperative course had been uneventful.

Apart from these instances, all the patients recovered, but postoperative complications were common (see table)—a fact which probably reflects the poor general condition of this group of patients before operation.

Discussion

The evidence from this review suggests that in about three-quarters of the patients the lesion responsible for the hæmorrhage will be found within the limits of a standard partial gastrectomy. This figure is less than that for the

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"blind" gastric resections which we have been able to analyse completely from published reports: in 36 of these an ulcer or erosion was identified in the resected specimen—a prevalence of just over 85%. This proportion is, however, unduly high because it includes 5 patients with juxta-œsophageal ulcer in whom reoperation was undertaken to remove the remaining portion of the stomach when bleeding continued postoperatively (Gilchrist and Chun 1954, Castagno and Hardaway 1958, Shuttleworth and Hull 1958). Of greater interest is the correspondence in age and sex between the patients in the present series and those recorded by others; it is clear that asymptomatic massive hæmorrhage for which surgery is required is not uncommon at, or past, middle age and that exploration and gastrectomy should not be long delayed in patients of this age-group. In our series of 31 patients operated on by a number of different surgeons but with skilled anæsthesia and the resources of an adequate transfusion service, the mortality was 10%; and the results of gastric resection in the hands of others have, on the whole, been comparable

PATIENTS SUBMITTED TO BLIND GASTRECTOMY FOR MASSIVE HÆMORRHAGE

Case no.	Age (yr.)	Sex	Presenting feature	Operation	Pathological findings	Result	Necropsy
1	38	F	Dyspepsia; hæmatemesis	Polya	3 superficial erosions lesser curve; chronic gastritis	Recovered	—
2	45	F	Hæmatemesis	Polya	Ulcer in line of section through lesser curve	,,	—
3	47	F	Dyspepsia; hæmatemesis	Billroth I	Acute gastric ulcer lesser curve	Recovered; deep vein thrombosis; laparotomy for necrosis of omentum	—
4	54	F	Hæmatemesis; aspirin	Billroth I	,, ,, ,, ,, ,,	Recovered; pneumonia and wound infection	—
5	58	F	Hæmatemesis; aspirin	Polya	,, ,, ,, ,, ,,	Recovered; rupture of duodenal stump	—
6	67	F	Hæmatemesis; dyspepsia; pain	Polya	,, ,, ,, ,, ,,	Recovered	—
7	35	M	Hæmatemesis and melæna; recurrent	Billroth I	,, ,, ,, ,, ,,	,,	—
8	47	M	Hæmatemesis	Polya	,, ,, ,, ,, ,,	,,	—
9	45	M	Hæmatemesis and melæna; recurrent	Billroth I	Multiple erosions of gastric mucosa	Recovered	—
10	47	M	Dyspepsia	Polya	Nil	,,	—
11	56	M	Dyspepsia; hæmatemesis	Polya	Nil	Death; intestinal pseudo-obstruction	No cause of obstruction or of hæmorrhage
12	54	M	Dyspepsia; pain; hæmatemesis	Billroth I	Nil	Recovered	—
13	63	M	Hæmatemesis; aspirin; coronary thrombosis (48 hr. before)	Polya	Acute gastric ulcer lesser curve	Recovered; deep vein thrombosis	—
14	65	M	Pain; hæmatemesis	Polya	Acute duodenal ulcer	Recovered	—
15	66	M	Pain; melæna	Polya	Chronic gastritis	,,	—
16	72	M	Dyspepsia and heartburn; hæmatemesis	Polya	Nil	Recovered; deep vein thrombosis	—
17	75	M	Recurrent hæmatemesis	Polya	Nil	Death; repeated hæmorrhage	Ulcer in duodenal stump
18	72	M	Hæmatemesis	Polya	Acute gastric ulcer posterior wall junction, upper and middle thirds	Recovered; personality changes (cerebral hypoxia)	—
19	48	M	Dyspepsia; hæmatemesis	Polya	Acute extensive duodenal erosion	Recovered	—
20	59	M	Dyspepsia; hæmatemesis	Polya	Acute gastric erosions	Recovered; deep vein thrombosis	—
21	20	M	Hæmatemesis	Polya	Multiple superficial erosions of body of stomach	Recovered	—
22	51	F	,,	Polya	Two acute ulcers of body of stomach	,,	—
23	45	M	,,	Polya	"Atrophic gastritis"; single large acute ulcer in anterior wall of stomach	,,	—
24	69	M	,,	Polya	Scar of old ulcer in antrum; no other source of bleeding	,,	—
25	74	F	,,	Polya	Two chronic superficial gastric ulcers on lesser curve	Died 3 days	Pulmonary embolus
26	65	F	,,	Polya	Gastric ulcer high on lesser curve	Recovered	—
27	57	F	,,	Polya	Chronic gastric ulcer 1 cm. diameter on lesser curve	,,	—
28	73	M	,,	Polya	Mild chronic gastritis	,,	—
29	80+	M	,,	Polya	Atrophic gastritis	,,	—
30	56	F	,,	Polya	Two acute ulcers in specimen	,,	—
31	65	F	,,	Polya	Multiple mucosal petechiæ; two small erosions	,,	—

with our own. The overall mortality for the many small reported series of primary gastrectomies† is 23% (14 deaths in 60 analysed cases); but these patients were often desperately ill and, like many with bleeding from a known source, had severe intercurrent cardiac or respiratory disease. Nevertheless, delay was often considerable and many patients had been repeatedly exsanguinated before surgery was eventually undertaken; there is little doubt that this must be of significance in determining the result. In the smaller series of patients who were treated conservatively or who were submitted to exploratory gastrotomy only, the results were poor. Of 16, 9 survived; in each of the 7 fatal cases a resectable ulcer was found at necropsy or at a second operation. It seems, as Ferguson (1953) has said, that in such circumstances the patient has been " put to the risk of operation and denied the possibility of benefit ".

Ætiology

Apart from the probable association already referred to between the acute gastric erosion and salicylate ingestion, little is known about the ætiology of the superficial gastric lesions. Some may occur in response to " stress " such as an operative procedure (McDonnell and McCloskey 1953) or childbirth (Castagno and Hardaway 1958), although the present series does not include such an instance. Nearly all the lesions are found on the lesser curvature or the posterior gastric wall, and it is the speed of erosion into submucosal vessels rather than the underlying vascular lesion which determines the rate and magnitude of bleeding (Osborn 1954). Although the lesion is superficial it may penetrate a moderately large vessel, the open end of which becomes fixed by fibrinoid necrosis in the base of the ulcer. In longitudinal-fissure ulcer of the œsophagogastric junction (Mallory-Weiss syndrome) there is good evidence that vomiting is not, as was originally thought, of ætiological significance (Shuttleworth and Hull 1958), and this lesion may be a special type of the proximal ulcer originally described by Dieulafoy (1898), and emphasised more recently by Gilchrist and Chun (1954), as an unrecognised source of bleeding. It is possible that case 17 was also of this type, and shortly after this study ended one of the units concerned encountered a further fatal example of the Mallory-Weiss syndrome.

The patient was a young man in whom subtotal gastrectomy was carried out. Bleeding recurred, and the patient could not be brought into a fit state for further surgery; the fissure at the cardiooesophageal junction was demonstrated at necropsy (J. A. Ross, personal communication).

Both lesions should be borne in mind if a patient bleeds after " blind " gastrectomy, and the successes recorded after total gastrectomy by Shuttleworth and Hull (1958) and Castagno and Hardaway (1958) underline the need for an aggressive surgical attitude.

Gastrotomy

In our series this was carried out only once. Information is available in 53 reported cases, in which it was done on 20 occasions. Of these it was positive in 15 and negative in 5; in these 5 the source of the bleeding was eventually found in the resected specimen or at necropsy. The procedure is thus no certain safeguard against error but, carefully performed, will more often than not yield positive information (Spencer and Maloney 1956). On the whole, however, we agree with Thieme (1954) that it may " unnecessarily prolong the operation in a poor risk patient " although it should undoubtedly be employed to examine the gastric or duodenal stump when no evidence of the source of the bleeding has been found in the resected specimen. One of the deaths in our series (case 17) would have been prevented by the adoption of such a policy. However, we do not feel that the identification by gastrotomy of a single cause of bleeding, such as a superficial gastric ulcer, justifies limiting the extent of the surgical procedure, because 8 of our 31 patients were shown to have multiple lesions in the resected specimen.

† The largest series is that of Spencer and Maloney (1956). Smaller numbers have been reported by Wangensteen (1945), Heuer (1946), Hall (1947), Crohn et al. (1948), Stewart et al. (1948), Ives (1949), Tanner (1951), Downie (1952), Ogilvie et al. (1952), Cooper and Ferguson (1953), Ferguson (1953, 1954), Gilchrist and Chun (1954), Sarason and Levy (1954), Thieme (1954), and Salasin and Bowers (1955).

Conclusions

This review presents the surgeon's viewpoint in massive gastrointestinal bleeding of unknown ætiology. Many of this group of patients, whose bleeding is less severe, recover with medical treatment, and their subsequent investigation and management have been reviewed by Avery Jones et al. 1959. Results suggest, however, that lack of a clear history of digestive upset does not preclude the existence of a superficial ulcer, usually gastric but occasionally duodenal, from which fatal bleeding will occur if gastrectomy is not undertaken. A subtotal gastric resection will remove the lesion in 75% of patients and will arrest the bleeding in the majority of the remainder. The overall mortality in this group should be no more than 10%. If massive bleeding continues after gastrectomy, only reoperation is likely to save the patient.

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" . . . I am, it is true, not certain that other people have consciousness. Neither indeed am I certain that the atomic nucleus exists. But I regard its existence as in the highest degree probable. I regard consciousness in other people as equally probable and for similar reasons. . . . We are all the time trying experiments on our relations with other people, informing, asking, ordering, obeying, resisting with varying emotions which are correlated with our actions. Human evolution has developed an elaborate and sensitive communication system, brought into play in innumerable ways. The hypothesis that other people have an interior life not unlike my own enables me to register correspondences at point after point in so intricate a way that I accept the hypothesis, if not as absolute truth, then as something nearly as good. And with most of the basic conclusions of science I am in no position to demand more."—Sir CYRIL HINSHELWOOD, P.R.S., anniversary address to the Royal Society, Nov. 30, 1959.

THE CASE AGAINST VASODILATOR DRUGS IN OCCLUSIVE VASCULAR DISEASE OF THE LEGS

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VASODILATOR drugs are widely advertised, are generously prescribed in obliterative vascular disease, and must account for a not inconsiderable part of the national drug bill. But are they in fact of any value in the treatment of patients with this condition? To relieve rest-pain or ischæmic skin lesions the drugs must increase blood-flow in the foot. To relieve claudication they must increase muscle blood-flow in the calf. In addition, their effect should be localised principally in the diseased limb, they should have a long action, and they should be effective when given by mouth.

As the blood-flow in the foot and calf can be measured, one need not speculate as to the probable clinical effect of these drugs, or attempt to assess their value in clinical trials. The measured change in blood-flow which they produce will at once indicate their usefulness; if they do not increase blood-flow they can have no therapeutic value. I present here such a quantitative investigation of the effect of vasodilator drugs on blood-flow in occlusive arterial disease of the legs under four headings—namely, their effect on blood-flow in the foot, their effect on muscle blood-flow, their value in augmenting the effect of sympathectomy, and their use in forecasting the result of lumbar sympathectomy.

Methods of Study

Blood-flow in the foot and calf of patients with and without obliterative arterial disease was measured by venous-occlusion plethysmography (Barcroft and Swan 1953), using water-filled plethysmographs at constant temperature in a constant-temperature laboratory. The blood-flow was measured at half-minute intervals. The resting flow was the mean of 20 consecutive measurements, and the postvasodilator blood-flow was calculated similarly fifteen minutes after intravenous injection of the drug.

The vasodilator drugs used were tolazoline ('Priscol'), phenoxybenzamine ('Dibenyline'), chlorpromazine ('Largactil'), and promazine—but this investigation represents the general physiological response to vasodilators in occlusive disease. In general, all three drugs had the same effect.

When blood-flow is measured as above the maximal flow produced by the drug is recorded; thus their vasodilator action has not been underestimated. Such flows are unlikely to be achieved and maintained in clinical practice.

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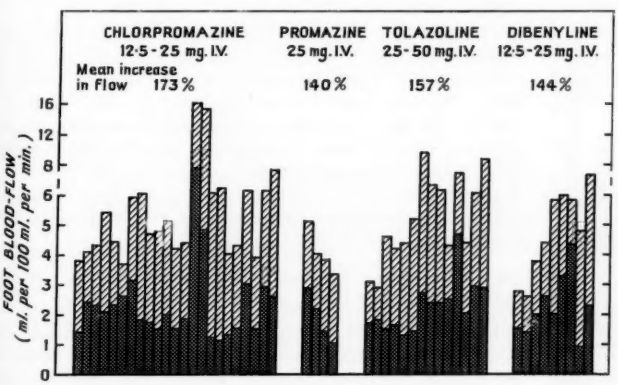

Fig. 1—Effect of vasodilators on the foot blood-flow in 50 normal limbs.

The hatched part of each column shows the resting flow, and the shaded part the increase in flow after the vasodilator was given. All flows are increased.

Findings

Are Vasodilators of Value in Patients with Ischæmic Skin Lesions or Rest-pain of the Feet?

A comparison of the effect of vasodilator drugs on the foot blood-flow in healthy limbs and in limbs with occluded arteries is of interest.

Fig. 1 shows their effect in healthy limbs. In all cases the flow increased, the maximum increase being 500%, and the mean 154%. There is thus no doubt as to the efficacy of vasodilators in increasing the flow of blood to the feet in healthy limbs, and this seems to justify amply their use in ischæmic disease. But the response in limbs with occluded arteries is quite different (fig. 2). In this case the patient had complete occlusion of the right femoral artery; the resting blood-flow in the feet was similar, but after the vasodilator was given there was the expected large increase in foot-flow in the normal left leg, but in the right leg the foot-flow became less. The effect of vasodilators on the blood-flow in the feet of 22 patients with arterial occlusions is illustrated further in fig. 3; to allow fair comparison of their effect, only patients with complete arterial blocks, demonstrated by aortography, were included. 15 had unilateral occlusion, and 7 bilateral occlusion. In 10 patients with unilateral occlusion the foot blood-flow in the affected limb was actually reduced by the drug. In all cases the foot blood-flow increased in the more normal limb. Foot blood-flow was reduced in both limbs in 3 patients with bilateral occlusions.

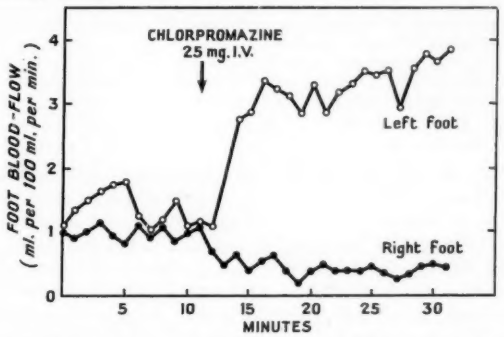

Fig. 2—Effect of a vasodilator on the foot blood-flow of a patient with right femoral artery occlusion.

While flow in the normal limb is increased, flow in the occluded limb is decreased.

Vasodilators are commonly thought to be harmless even if they do no good, but these results suggest that they may reduce seriously an already poor blood-flow to the foot in occlusive vascular disease. What physiological mechanism causes the fall in blood-flow in a limb with an occluded artery after a vasodilator has been given? When the drug is given by mouth or intravenously, vasodilatation occurs in many areas due to a general reduction in peripheral resistance. Thus blood is redistributed (De Bakey et al. 1947), but, owing to the arterial occlusion, that destined for the diseased limb can pass elsewhere more easily, and so the blood-flow beyond the obstruction may actually be reduced. If the systemic blood-

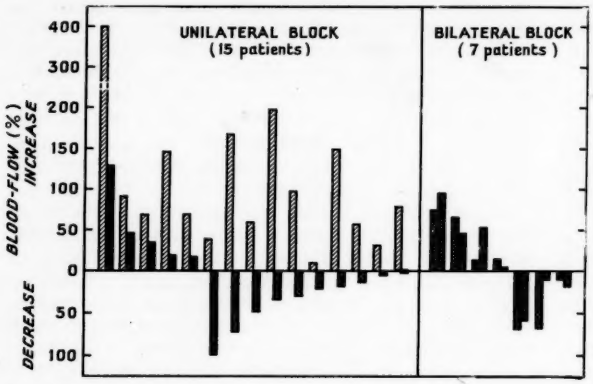

Fig. 3—Effect of vasodilators on the foot blood-flow of 22 patients with complete arterial occlusions.

The flow in occluded limbs is shown by hatched columns, and in non-occluded limbs by shaded columns. The flow is decreased more often than increased in the occluded limbs.

pressure is lowered by the vasodilator, as happens frequently, filling of the arterial tree distal to the block may be reduced further. In this connection Dornhorst and Sharpey-Schafer (1951b) pointed to the blanching of the foot in some patients at the onset of claudication, offering the explanation that the local blood-pressure beyond the block falls when the general peripheral resistance decreases during exercise. Boyd (1956) has summed up graphically the effect of vasodilators on blood-flow in limbs with occluded arteries by remarking:

"Opening the taps wider (i.e., peripheral vasodilatation) will not alter the rate at which the bath fills if the water is turned off at the main."

Blood-flow studies give little support to the use of vasodilator drugs in the treatment of the ischæmic foot in occlusive arterial disease.

Are Vasodilators of Value in Intermittent Claudication?

Intermittent claudication is prone to such spontaneous variations in severity that the result of clinical drug trials must be interpreted with caution. If vasodilators are to relieve claudication they must increase muscle blood-flow; and their ability to do this can be measured.

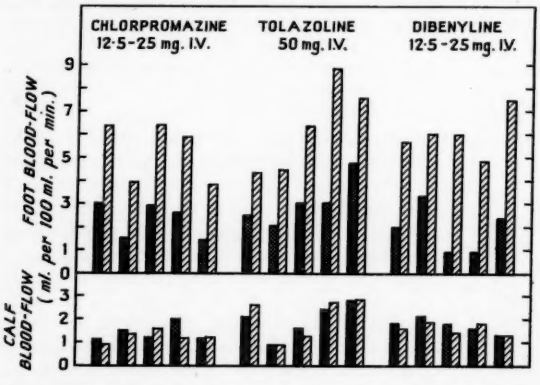

Fig. 4—Effect of vasodilators on the foot and calf blood-flows, recorded simultaneously, of 15 normal subjects.

The hatched columns show the blood-flow before and the shaded columns the flow after vasodilators were given. The foot-flow is increased in all cases, but the overall effect on calf-flow is a decrease of 4%.

The effects in 15 normal subjects of various vasodilators on blood-flow in the foot and calf, recorded simultaneously, are set out in fig. 4. In every case the foot-flow increased, the mean increase being 147%. The effect on muscle blood-flow, however, was small and variable, the overall change being a mean decrease of 4%. Other workers also have reported a fall in muscle blood-flow after vasodilators (Lynn 1950, Murphy et al. 1950, Hensel et al. 1955). If vasodilators do not increase calf blood-flow in patients with normal arteries they are unlikely to do so in patients with occluded arteries. This is shown in table I; the patient had bilateral calf claudication and bilateral arterial occlusions, and the blood-flow in both foot and calf was reduced after the vasodilator was given.

The slight effect of vasodilators on muscle-flow is hardly surprising when one recalls that blood-flow in muscle vessels is controlled largely by local metabolites, and is hardly influenced by nervous stimuli (Goetz 1949, Barcroft 1952). Indeed, sympathectomy itself, though localised in effect to a single limb, causes no lasting increase in muscle blood-flow in limbs with patent or occluded arteries, either at rest or in activity (Grant and Holling 1937, Stein et al. 1948, Shepherd 1950, Duff 1951), and no more than a transitory decrease in collateral resistance in occluded limbs (Dornhorst and Sharpey-Schafer 1951a and b). If sympathectomy does not increase muscle blood-flow, vasodilator drugs are unlikely to do so. The probable physiological reason for the fall in muscle blood-flow at rest after a vasodilator is given is that blood is diverted from the muscles into the now widely opened cutaneous vascular bed; a similar fall occurs during reflex heating (Edholm et al. 1956).

TABLE I—EFFECT OF A VASODILATOR ON THE BLOOD-FLOW OF THE FOOT AND CALF IN A PATIENT WITH BILATERAL ILIAC AND FEMORAL ATHEROSCLEROSIS

Part	Blood-flow (ml. per 100 ml. per min.)		Decrease in flow (%)
	At rest	After vasodilator (chlorpromazine 25 mg. I.V.)	
Right foot ..	3·4	3·0	12
Left foot ..	1·7	1·4	18
Right calf ..	2·4	1·9	21
Left calf ..	1·9	1·4	26

The results of my experimental studies support the views of Richards (1957), that fluctuations in the severity of claudication represent the natural history of the disease rather than the result of drug treatment, and of Semple (1953), that the improvement reported after giving vasodilators "is no more than would have resulted from conservative treatment and the passage of time".

Blood-flow studies do not support the use of vasodilator drugs in the treatment of patients with intermittent claudication.

Do Vasodilators Augment the Blood-flow in Limbs Sympathectomised for Occlusive Arterial Disease?

One is tempted to try to supplement the effect of sympathectomy on blood-flow by giving a vasodilator drug after operation (*Lancet* 1951). On physiological principles, however, this is unlikely to succeed. A sympathectomy is limited in its effect to reducing peripheral resistance in a single limb, so that this limb gains a selective-filling advantage, and its blood-flow increases.

But if a vasodilator is given, peripheral resistance is reduced in all the other limbs and blood is redistributed, the sympathectomised limb losing its filling advantage. The amount of blood it receives thus tends to be reduced. This may be expected whether sympathectomy was done for obliterative or vasospastic disease.

Fig. 5 shows the typical effect of a vasodilator drug on blood-flow in a sympathectomised foot. Unilateral sympathectomy had been done for vasospastic disease in which the vessels are fully capable of vasodilatation. Neither the vasodilator nor reflex heating caused any rise in blood-flow; indeed, the flow was reduced. In the non-sympathectomised limb there was a large increase in blood-flow. The effects of vasodilators on foot blood-flow in 29 legs, sympathectomised four days to seven years previously for atherosclerosis, were studied also

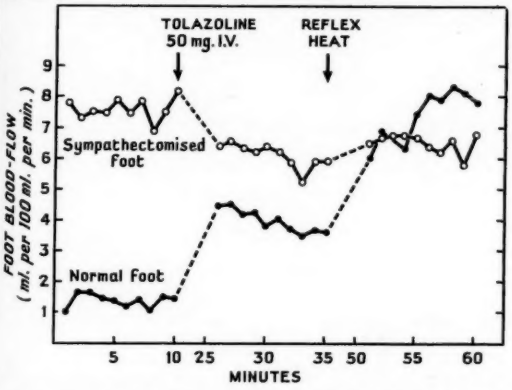

Fig. 5—Effect of a vasodilator and reflex heating on the foot blood-flows of a patient with unilateral lumbar sympathectomy for vasospastic disease.
Flow in the sympathectomised foot is decreased.

(fig. 6); in 25 of these limbs there was a decrease, or no significant increase, in blood-flow.

Vasodilators (oral or intravenous), therefore, should not be used in an attempt to increase the blood-flow in a limb sympathectomised for occlusive arterial disease because they are most likely to reduce the flow.

Does the Response to Vasodilator Drugs Indicate the Probable Effect of Sympathectomy in Occlusive Vascular Disease?

The response to a vasodilator drug has been suggested as a useful indication of the probable effect of sympathectomy (Lynn 1950, Duff et al. 1956). But this is only

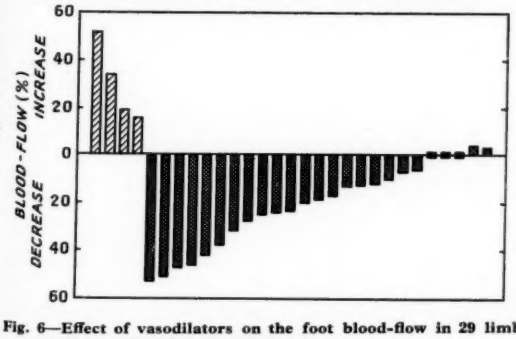

Fig. 6—Effect of vasodilators on the foot blood-flow in 29 limbs sympathectomised for atherosclerosis.
The percentage increase or decrease in blood-flow produced by chlorpromazine, tolazoline, or phenoxybenzamine is shown by a column above or below the baseline. Most flows are decreased.

TABLE II—RESPONSE TO VASODILATOR DRUGS BEFORE SYMPATHECTOMY, AND THE EFFECT OF SYMPATHECTOMY IN THE LIMB STUDIED

—	Case 1 (aged 66)	Case 2 (aged 49)
Effect of vasodilator on foot blood-flow	Chlorpromazine 25 mg. I.V. 13% decrease	Phenoxybenzamine 25 mg. I.V. 5% decrease
Effect of sympathectomy on foot blood-flow	100% increase	109% increase

true in vasospastic disease. As already pointed out, such a test is not based on sound physiological grounds when applied in obliterative disease. Because the vasodilator has a generalised effect, and sympathectomy has a localised one, the vasodilator will not indicate the effect of sympathectomy.

This is shown in 2 patients (table II) with unilateral arterial occlusion. In both, the blood-flow in the affected limb was reduced by the vasodilator, but lumbar sympathectomy greatly increased it.

The response to vasodilator drugs thus gives no indication of the probable effect of sympathectomy in occlusive vascular disease, and is valueless as a pre-operative test. For the same reasons the response to reflex heating of the body may be equally fallacious (Learmonth et al. 1944).

Conclusions

Certain clinical conclusions as to the value of vasodilator drugs in occlusive arterial disease of the legs can be drawn from these blood-flow studies:

1. Vasodilator drugs are not likely to increase blood-flow in the ischæmic foot, and the fall in blood-flow which often follows their administration could prove disastrous to the critically nourished foot after an acute occlusion. Whether given by mouth or intravenously, they have no place in the treatment of acute arterial occlusion, or of the chronically ischæmic foot.
2. As vasodilators do not increase calf-muscle blood-flow, and often decrease it, prescribing them for intermittent claudication is useless.
3. Vasodilators usually decrease blood-flow in a sympathectomised limb, and therefore should not be used in an attempt to augment the effect of sympathectomy.
4. Finally, the response to a vasodilator drug gives no indication of the response to sympathectomy. Such a pre-operative test is valueless and may lead to a suitable patient being refused operation.

Much unnecessary prescribing and expense would be saved if these observations were recognised.

I should like to thank Prof. D. M. Douglas for his interest and encouragement; Miss Margaret Mackenzie for help with the figures; and Mr. William Muir for much technical assistance. Messrs. Smith, Kline & French kindly supplied the 'Dibenyline'.

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INTER-RELATION OF VITAMIN B_{12} AND IRON

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This investigation was undertaken to explain the finding of subnormal serum concentrations of vitamin-B_{12} in a number of patients with iron-deficiency anæmia. We studied the response to therapy in thirteen such patients, and compared it with the response in other patients who had iron-deficiency anæmia but normal B_{12} levels. Patients with acute blood-loss were studied in a similar way.

Serum-iron was estimated by the method of Ramsay (1957), and serum-B_{12} microbiologically with *Lactobacillus leichmannii* (Meynell et al. 1957). Changes in the blood-picture and the response to therapy were determined by routine hæmatological methods. Serum-B_{12} levels were assayed before beginning therapy, and at frequent intervals during and after hæmatological remission.

The Patients

Table I gives the details of the patients with subnormal serum-B_{12} levels. The bone-marrow showed no evidence of megaloblastic erythropoiesis, though two patients had some macronormoblasts and three showed occasional giant metamyelocytes. Six had had a partial gastrectomy, two had a hiatus hernia, two a long history of menorrhagia, and two a long history of malnutrition. In all there was evidence of long-standing iron deficiency. During iron therapy, they continued to take their accustomed diet.

The hæmatological picture of these thirteen patients with low serum-B_{12} levels did not differ significantly from that in the twelve patients with iron deficiency and normal serum-B_{12} levels (table II). Only two of those with low serum-B_{12} levels had a macrocytic anæmia, and all of both groups showed definite hypochromia. The three with acute hæmorrhage from a peptic ulcer, who had normal B_{12} levels, were compared with three with a history of repeated intestinal hæmorrhages, and one other who had been passing tarry stools for nearly 10 weeks, all of whom had subnormal B_{12} levels

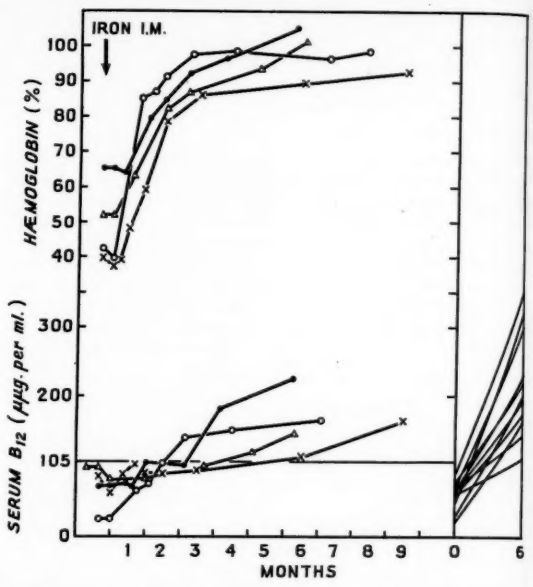

Fig. 1—Changes in hæmoglobin and serum-B_{12} in four patients with iron and B_{12} deficiency following intramuscular iron. Inset diagram shows the changes in twelve patients before and 6 months after commencing iron therapy (normal serum-B_{12} is 105 μμg. per ml. and over).

Results

All the patients achieved normal blood-levels on iron therapy alone. In the thirteen patients whose serum-B_{12} was initially low, it returned to normal levels;

TABLE I—PATIENTS WITH IRON-DEFICIENCY ANÆMIA AND SUBNORMAL SERUM-B_{12} LEVELS

Patient no.	Sex	Age	Red-cell count (×10⁶ per c.mm.)	Hb (g. per 100 ml.)	White-cell count (per c.mm.)	Packed-cell volume (%)	Mean corpuscular volume (cμ)	Mean corpuscular hæmoglobin concentration (%)	Serum-Fe (μg. per 100 ml.)	Serum-B_{12} (μμg. per ml.)	Ætiology
1	F	27	4·31	10·3	6000	34·5	80	30	24	75	Idiopathic
2	F	49	4·17	10·7	5300	35	85	31	28	100	Partial gastrectomy
3	F	47	3·90	7·0	3800	30	77	23	28	25	Partial gastrectomy
4	F	40	3·73	5·8	4700	28·5	77	20·5	13	25	Chronic menorrhagia
5	F	76	3·56	5·8	3200	22·5	64	26	13	62	Hiatus hernia
6	F	39	4·44	6·5	6400	25	56	26	11	85	Menorrhagia and poor diet
7	F	44	4·45	9·7	5000	37	83	26·5	13	70	Poor diet
8	M	50	3·80	7·0	5500	28	73	25	18	100	Partial gastrectomy
9	F	66	3·04	8·9	7200	34	112	27	16	75	Hiatus hernia, poor diet
10	F	64	4·15	8·3	7200	30	73	27·5	23	65	Partial gastrectomy
11	M	54	1·40	4·3	5600	13	90	30	14	62	Poor diet
12	M	18	4·38	9·2	6500	31	71	30	18	70	Regional ileitis
13	M	62	3·20	4·8	6000	..	..	..	..	30	Partial gastrectomy

TABLE II.—PATIENTS WITH IRON-DEFICIENCY ANÆMIA AND NORMAL B_{12} LEVELS

14	M	56	3·24	6·3	6000	24·5	76	25	11	285	Partial gastrectomy
15	F	42	4·59	7·1	10,200	30	66	23·5	8	245	Menorrhagia
16	F	58	2·60	3·8	3000	18	70	21	8	175	Poor diet, varicose ulceration
17	F	30	4·31	9·2	4800	35·5	82	26	10	175	Partial gastrectomy
18	F	42	3·55	7·7	7400	28	79	27·5	9	190	Poor diet
19	F	76	3·48	5·2	5400	25	72	20	12	240	Hiatus hernia
20	F	38	5·02	8·3	9800	34	68·5	24·5	18	230	Blood-donor
21	F	22	4·72	9·7	5000	36	77	29	38	240	Menorrhagia
22	F	56	3·72	9·4	6600	32·5	88	29	16	135	Hiatus hernia
23	F	29	4·18	7·2	6000	29	70	24·5	18	..	Proctosigmoiditis
24	F	50	2·66	4·6	7200	17·5	66	24	14	250	Severe varicose ulceration
25	F	76	3·93	5·6	5300	24·5	61	23	9	280	Idiopathic

but in all but one of them the return was slow, with low levels persisting after at least 10 weeks' iron therapy. (Four typical examples are shown in fig. 1) The exception (patient no. 10) showed a return of the serum-B_{12} to the lower limits of normal (105 μμg. per ml.) 19 days after the commencement of 'Imferon' 5 ml. intramuscularly on alternate days. 3 days later the B_{12} level was 140 μμg. It subsequently fell to 115 μμg. and then rose again within 6 weeks of commencing iron therapy to 200 μμg. per ml. These variations are somewhat similar to those seen in patients with normal serum-B_{12} levels while on iron therapy.

Four curves showing the alterations in serum-B_{12} levels during an iron-induced remission in this latter group are shown in fig. 2. A and B are the extremes observed, while C and D are typical examples. In all the twelve patients studied a rise of the serum-B_{12} level of over 50 μμg. per ml. occurred within 10 days of commencing therapy. This was usually followed by a fall, in some instances to below pre-treatment levels. Later a similar rise and fall were noted, the latter coincident with attainment of normal blood-levels. There was an identical rapid rise in serum-B_{12} levels in patients with acute hæmorrhage, but with no history of previous episodes and presumably with normal B_{12} levels at that time.

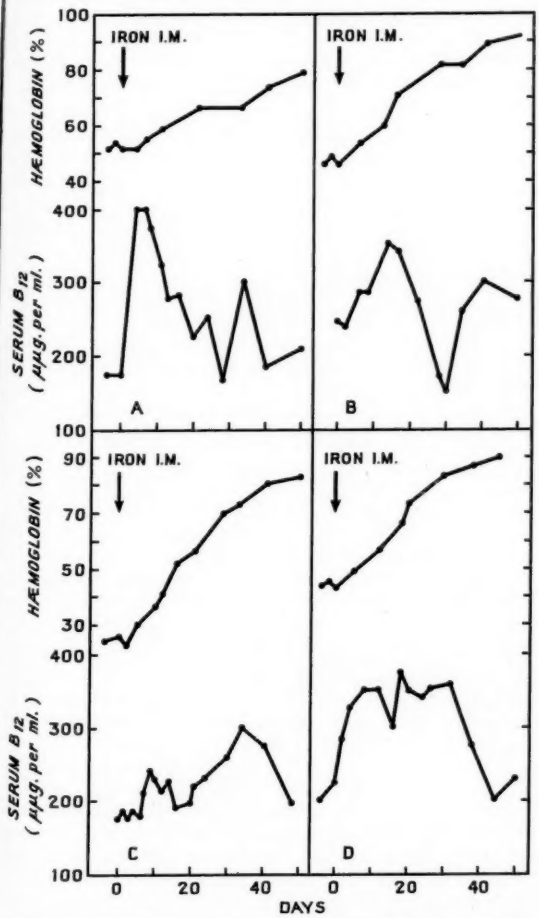

Fig. 2—Changes in hæmoglobin and serum-B_{12} during iron therapy in four patients with iron deficiency and normal serum-B_{12} levels.

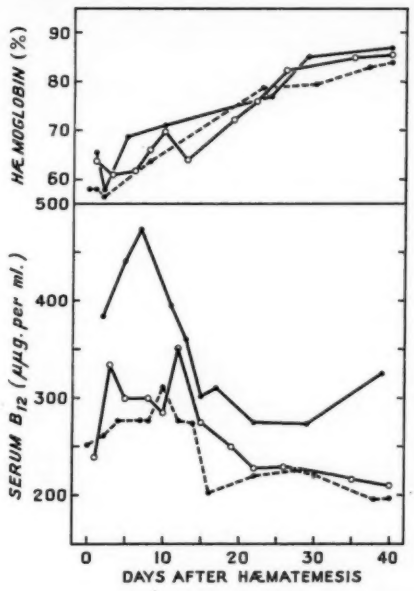

Fig. 3—Changes in hæmoglobin and serum-B_{12} levels in three patients after an acute blood-loss.

This initial rise might perhaps be greater if the serum-B_{12} level was determined on a specimen of blood taken immediately after the onset of hæmorrhage. Such a suggestion is strengthened by the fall of B_{12} after hæmatological remission to below the initial level (fig. 3).

On the other hand, three patients (fig. 4) who presented after acute episodes of alimentary bleeding and had low serum-B_{12} levels did not show a rapid rise of B_{12}

Serum-levels gradually rose to normal in 10, 15, and 18 days. Two of these patients had a history of repeated hæmorrhage and the third had been passing dark stools intermittently for 10 weeks. The patient, who was transfused to normal levels (fig. 4) had a further small intestinal bleed not requiring readmission, 2 months after his serum-B_{12} had returned to normal. Again the serum-B_{12} fell to subnormal levels. Patient no. 2, who incidentally had had a low serum-B_{12} with hypochromic anæmia and required 10 weeks to achieve normal blood-levels on iron by mouth, had a hæmatemesis 5 months later: the hæmoglobin fell to 68%, and the serum-B_{12} fell to below normal levels and remained low for 6 weeks.

Discussion

It is of interest that pioneer workers on B_{12} assay observed among their controls subjects with abnormally low serum-B_{12} levels (Mollin and Ross 1952). Girdwood (1954) records a patient with a refractory iron-deficiency anæmia and a low serum-B_{12} level. In a randomly selected group Spray and Witts (1958) observed two patients who had had a partial gastrectomy 5 years previously, and who had low serum-B_{12} levels. These findings were attributed to chance, experimental error, or the vagaries of microbiological assay. Thus, quite erroneously, it has become accepted that B_{12} deficiency, as indicated by low levels in the serum, is always associated with bone-marrow changes. That this is incorrect is amply borne out by our results.

The finding of subnormal serum-B_{12} levels in patients with iron-deficiency normoblastic anæmia caused by repeated acute blood-loss must mean either that the

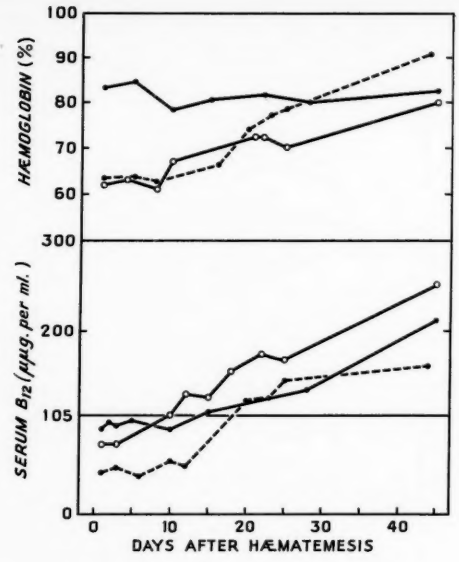

Fig. 4—Changes in hæmoglobin and serum-B_{12} levels in three patients who had subnormal B_{12} levels after blood-loss. Patient was transfused with 5 pints of blood, shortly after admission (normal B_{12} is 105 μμg. per ml. and over).

serum-B_{12} level is not an accurate measure of the body stores, or that a deficiency of vitamin B_{12} can occur without either neurological or hæmatopoietic abnormalities. In our patients, the slow return of the serum-B_{12} level to normal, after hæmatological remission with iron therapy, suggests that a failure of absorption has been corrected. This hypothesis is supported by the more rapid return of the serum-B_{12} level to normal in patients with anæmia due to blood-loss, probably as a result of mobilisation of B_{12} from the tissues. Mixed blood-pictures of chronic iron deficiency and acute blood-loss may account for the somewhat intermediate results observed in patients nos. 2 and 11. This implies that the serum-B_{12} in partially depleted patients may be temporarily lowered to subnormal levels by acute hæmorrhage, and that the rate of its return to normal will depend on the degree of deficiency. Though a mobilisation of B_{12} stores after acute hæmorrhage may partly explain the rise in serum-B_{12}, this cannot be the whole answer, since the B_{12} changes are different in patients with normal B_{12} levels and iron deficiency either remitting from acute blood-loss or responding to treatment of iron-deficiency anæmia. In these non-B_{12}-deficient cases, a surge of B_{12} activity occurred in association with increased erythropoiesis, as judged by the improving blood-picture. The surge fluctuated until remission was achieved. We observed it in only one B_{12}-deficient patient, but in some of the earlier cases our observations may not have been made soon enough. An increase in the serum-B_{12} activity has been noted by Narayanan et al. (1956) after folic-acid therapy in non-B_{12}-deficient nutritional megaloblastic anæmia, and we have made similar observations on megaloblastic anæmia of pregnancy and on the anæmia associated with adult cœliac disease (Cox et al. 1959c). Thus it seems that when there is no depletion of vitamin B_{12}, serum-activity increases during blood regeneration induced by hæmorrhage, folic acid, or iron therapy.

Most iron-deficient patients with a low serum-B_{12} have an actual deficiency of B_{12}. Not only is recovery slow with iron therapy, but in five of these patients the B_{12} content of the buffy-coat layer of the sternal-marrow aspirate and of the serum was indistinguishable from those found in addisonian pernicious anæmia in relapse (Cox el al. 1959b).

The most likely explanation of this B_{12} deficiency is defective absorption.

Malutilisation could hardly be the mechanism, since patients with a similar clinical and hæmatological picture have normal serum-B_{12} levels. Witts (1956) has stated that iron deficiency can cause chronic atophic gastritis. The degree of gastric atrophy may be as severe as that seen in pernicious anæmia (Badenoch et al. 1955, Davidson and Markham 1955, Joske et al. 1955); in fact two of the cases reported by Badenoch et al. (1955) had low serum-B_{12} levels. The secretion of intrinsic factor may be impaired in severe iron deficiency (Hartfall and Witts 1933), an observation which has been confirmed in man using radioactive vitamin B_{12} (Badenoch et al. 1957) and in rats (Taylor and Witts 1958). Callender (1958) has stated that, in patients with iron-deficiency anæmia in whom vitamin-B_{12} absorption was impaired, no improvement in absorption of vitamin B_{12} had been observed after recovery from the iron deficiency.

The effect of the chronic iron deficiency is probably greater in patients with abnormal stomachs, which accounts for the high incidence of patients with partial gastrectomy in our B_{12}-deficient group. Lowenstein (1958) found that of twenty-two patients with partial gastrectomies only three (two with severe iron deficiency) had abnormally low B_{12} absorption.

If the B_{12} depletion in our patients is due to a deficiency of intrinsic factor as a result of chronic atophic gastritis, then this deficiency must be reversible, since the serum-B_{12} level rises following iron therapy. The condition we describe differs from pernicious anæmia, in which, by the definition of Davis and Brown (1953), there is an irreversible deficiency of intrinsic factor. Because of the high metabolic activity of the intestinal cells, other functions of the small intestine may be impaired, even fat absorption. We have recently observed a group of patients with chronic iron deficiency and unexplained steatorrhœa (Cox et al. 1959a); examples of such patients are given in tables I and II (patients nos. 5, 6, 9, 19, and 22). Moreover, even with adequate amounts of intrinsic factor B_{12} absorption may be depressed temporarily.

It should be pointed out that all ten of our patients with B_{12} deficiency and hypochromic anæmia who were tested had no free acid in the gastric contents after histamine stimulation: such patients could be examples of incipient pernicious anæmia. Many have suggested that chronic iron deficiency may be an ætiological factor in pernicious anæmia, particularly in those patients in whom it has been observed to precede pernicious anæmia (Campbell and Conybeare 1922, Witts 1930, Dameshek 1931, Miller and Dameshek 1941, Mosbech 1953, Nelson and Weaver 1956). Nevertheless the " gastric lesion " in all our patients must still be reversible and restored to normal by therapy with iron.

Summary

In thirteen patients with iron-deficiency normoblastic anæmia was associated with low serum-B_{12} levels. In all of them the serum-B_{12} returned to normal under iron treatment; but in all but one this took at least 10 weeks. The explanation suggested is that these patients had an actual deficiency of B_{12} which was restored when B_{12} absorption was corrected by iron therapy.

Three patients with low serum-B_{12} levels associated with repeated or chronic alimentary bleeding showed a quick return of the B_{12} levels—in 10, 15, and 18 days. The patients with low serum-B_{12} levels differed from similar patients with normal levels in that they did not show the increase and subsequent changes in the serum-B_{12} levels observed with blood regeneration after the correction of an iron deficiency or after acute blood-loss.

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URINARY INFECTION IN THE NEWBORN *

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MICTURITION symptoms are unusual in young children with urinary infections. In the first year of life such infections often give rise to feeding difficulties, apathy, anorexia, a heavy neonatal weight-loss, and a slow return to birthweight, whereas in older children the infection may induce persistent enuresis. Fever and convulsions are sometimes seen.

Urinary infection tends to relapse in infants; and this, together with the patients' failure to thrive in the early weeks of life, raises the question whether many infections begin in the neonatal period and remain unrecognised until a dramatic episode of vomiting, fever, or convulsions leads to examination of the urine. It therefore seemed worth investigating the urine of newborn babies whose progress, for no obvious reason, was not satisfactory.

Material and Method

Stansfeld (1954) adopted a routine of counting pus cells in a cubic millimetre of uncentrifuged urine and found that in boys of all ages and in infants of either sex the urine usually contained less than 10 pus cells per c.mm. More than 50 cells per c.mm. were rarely found in the absence of renal-tract disease. It seemed possible, however, that this generalisation might not be valid for newborn infants; and I therefore decided to investigate the urine of normal newborn babies before embarking on a study of urinary infection.

Normal Babies

Urine was collected from 50 male and 50 female babies, between 6 and 10 days old. Each specimen was taken into a sterile container immediately after a feed and examined shortly after collection; pus cells per c.mm. uncentrifuged urine were counted in a white-cell counting-chamber and cultures were made also from a random sample of uncentrifuged urine.

* Based on a paper read to the British Pædiatric Association in April, 1958.

TABLE I—ORGANISMS CULTURED FROM THE URINES OF 100 HEALTHY INFANTS

—	Sterile	Growth		
		Scanty	Moderate	Heavy
No. of patients	4	82	9	5
Organisms	..	*Esch. coli* (82)	*Esch. coli*	*Esch. coli*
	..	*Esch. coli* plus *Str. fæcalis* (16)		

Table I shows that in most boys the pus-cell count was below 25 per c.mm. In 1 it reached 125 per c.mm., but twenty-four hours later it had fallen to 20. In 3 cases the pus-cell counts were above 1000: twenty-four hours later each of the babies deteriorated—they began to lose weight, refused feeds, and became apathetic, and 1 developed a fever of 102°F. Urines were collected again and the pus-cell counts were 4800, 1150, and 1200 respectively. These babies were considered to have urinary infections.

Higher pus-cell counts were found among the girls: most had up to 50 pus cells per c.mm. uncentrifuged urine. In 11 the counts were higher; but they returned to normal on the next day. This showed the importance of collecting more than one specimen in cases of doubt, since contamination with vaginal secretions may lead to inaccuracy.

All specimens were cultured; and only 4 were sterile. In most specimens the growth was scanty: in some it was heavy, and a few yielded contaminants (table I).

Babies with Urinary Infection

32 infants with urinary infection—1·5% of all live births in the hospital during the period under review—were studied. There were 19 females to 13 males, and the age at onset was between 6 and 12 days.

Diagnosis

The clinical picture was often far from striking. Failure to gain weight, loss of weight, apathy, and anorexia were the most common symptoms which led to examination of the urine (table II). Local œdema of the vulva was seen in only 3 of the girls. None of the boys had been circumcised.

The diagnosis rested upon the pus-cell count in uncentrifuged urine together with a positive culture. Usually with up to 500 pus cells per c.mm. there was a moderate growth, whereas urine containing more cells yielded a heavy growth of organisms. Second specimens were examined whenever there was lack of correlation between the pus-cell count and the cultures.

The blood-urea was estimated in 17 cases. In 5 it was between 50 and 76 mg. per 100 ml.; but, when estimated again some weeks later, it had fallen to normal levels.

Escherichia coli was grown in pure culture in 26 cases; *Esch. coli* and *Proteus vulgaris* together in moderate growth in 2 cases; and in 2 cases there was a heavy growth of both organisms. *Staphylococcus aureus* was grown in pure culture in 1 case; and from another a pure and heavy growth of *Pseudomonas pyocyanea* was isolated.

Management

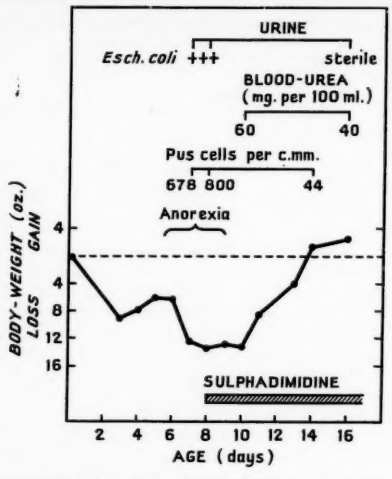
Treatment

Rapid clinical improvement usually began after forty-eight hours' therapy: appetite returned and weight started to increase (see figure). Those babies whose blood-urea

TABLE II—SYMPTOMS OF URINARY INFECTION IN THE NEWBORN

Symptom	No. of cases
Loss of weight	31 (97%)
Anorexia	20 (62·5%)
Apathy	20 (62·5%)
Fever	5 (15·5%)
Vomiting	3 (10%)

was raised were slower to respond. Birthweight was regained in most cases at 21 days. Tube feeding was necessary in 4 babies, and hand-feeding rather than breast-feeding was resorted to in 12 of the remaining 28. Breast-feeding was established again after three or four days.



Urinary infection in a boy aged 6 days. He was breast-fed for a week but hand-fed with expressed breast-milk on the eighth and ninth days.

7 babies were treated with sulphadimidine and 21 with 'Sulphatriad' in doses of 1 g. daily for fourteen days. This course was followed in all cases by another course of sulphonamide 0·25 g. daily for four weeks.

In 1 patient sulphadimidine was given for one week only: the child relapsed four days later and was then treated for the full two weeks. 2 cases of mixed *Esch. coli and Pr. vulgaris* infection relapsed a few days after the completion of their six-week course. Both were treated for another twelve weeks and have not relapsed since (two-year follow-up).

3 babies were given intramuscular streptomycin 20 mg. per lb. body-weight daily for a week. In 1 the *Esch. coli* was resistant to sulphonamide, and in the other 2 the urine contained a heavy growth of both *Esch. coli* and *Pr. vulgaris*. 1 patient whose infection was caused by *Ps. pyocyanea* was given nitrofurantoin ('Furadantin') 20 mg. daily for ten days, since the organism was sensitive only to this drug and to chloramphenicol. These 4 infants were also given a subsequent course of sulphonamide 0·25 g. daily for 4 weeks.

Follow-up

Each child was followed up at the outpatient clinic at fortnightly intervals for three months, and thereafter at three-monthly intervals. Up to the time of writing, patients have been followed for a minimum period of a year and a maximum period of two years and nine months. 2 girls relapsed a few days after the end of their six-week course of treatment, but they responded to a further three months' chemotherapy.

Discussion

Increasing attention has been paid in recent years to urinary infection in infancy, and it is becoming more widely realised that the clinical picture is misleading. Symptoms are seldom referable to the urinary tract, and pyuria is often difficult to demonstrate (Stansfeld 1954). It has long been taught that girls are affected more often than boys, but in this series the sex difference was not significant (girls/boys: 1·4/1). It seems probable that the infection was usually hæmatogenous rather than ascending.

Asphyxia was no more common in the infected than in the healthy babies born in the same hospital during the same period; nor were the artificially fed babies especially prone to infection. None of the babies was wholly bottle-fed at the onset of symptoms.

Treatment and supervision must continue for a long time (Giles and Porter 1956). In an earlier series chemotherapy was given for only a week or ten days; and 7 out of 21 babies had one or more recurrences. In the present series treatment was given for six weeks (two weeks' full dosage, and four weeks' smaller dosage) with only 3 recurrences. Excluding a baby who inadvertently received only a week's treatment, the relapse-rate was 6·2%, compared with 33% after the shorter course. I would agree wholeheartedly with Smallpeice (1958) that children who have had pyuria at any time should receive no chemotherapy for any subsequent illness until the urine has been collected for microscopical examination.

Urinary infection, especially when recurrent, may be associated with congenital anomalies of the renal tract. No such defects have been detected so far in these 32 children; but they are often difficult to demonstrate, and pyelography has not yet seemed justified in any of the patients. Supervision over many years will be necessary before an accurate prognosis can be given.

Summary

A white-cell count of uncentrifuged urine is indicated whenever urinary infection is suspected in the newborn. Uncentrifuged urine from normal female infants contains less than 50 white cells, and from normal male infants less than 25 white cells, per c.mm.

The symptoms of urinary infection in the newborn are loss of weight, anorexia, and apathy. Fever and vomiting are occasionally seen.

Treatment should be continued for six weeks. The children should be followed-up for a number of years.

My thanks are due to the staff of the Louis Jenner Laboratory of St. Thomas's Hospital, and particularly to Mr. R. Lynn, for the pathological investigations; and to the resident medical staff of the General Lying-In Hospital for their case-records. I am particularly indebted to the sisters and nurses for their cooperation and skill in the collection of the specimens.

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5-HYDROXYTRYPTOPHAN AS AN INTERMEDIATE OF SEROTONIN BIOSYNTHESES IN MALIGNANT CARCINOIDOSIS

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THE studies of Udenfriend et al. (1956) and Davidson et al. (1957) suggest that in the body the first step in the formation of serotonin is the hydroxylation of tryptophan to form 5-hydroxytryptophan (5-H.T.P.). The presence of 5-H.T.P. in the urine of a patient with malignant carcinoidosis has been reported (Sandler and Snow 1958), but, though the conversion of tryptophan to 5-H.T.P. has been demon-

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PAPER CHROMATOGRAPHIC SEPARATION OF THREE NITROSONAPHTHOL-REACTING SUBSTANCES DEMONSTRABLE IN THE URINE OF TWO PATIENTS

—	R_f in solvent 1	R_f in solvent 2	R_f in solvent 3	R_f in solvent 4
5-H.T.P.	0·11 (0·09–0·15)	0·17 (0·14–0·19)	0·29 (0·26–0·34)	0·46 (0·41–0·49)
Patient no. 1	0·10 (0·08–0·15)	0·17 (0·13–0·19)	0·28 (0·25–0·32)	0·46 (0·44–0·48)
Patient no. 2	0·11 (0·10–0·12)	0·18 (0·15–0·20)	0·28 (0·27–0·30)	0·47 (0·43–0·50)
5-H.T.	0·52 (0·48–0·56)	0·56 (0·55–0·57)	0·43 (0·39–0·46)	0·37 (0·33–0·41)
Patient no. 1	0·50 (0·46–0·54)	0·55 (0·53–0·57)	0·43 (0·41–0·45)	0·38 (0·35–0·41)
Patient no. 2	0·53 (0·49–0·55)	0·56 (0·52–0·59)	0·41 (0·38–0·43)	0·37 (0·34–0·43)
5-H.I.A.A.	0·14 (0·10–0·16)	0·74 (0·71–0·76)	0·82 (0·76–0·86)–	0·56 (0·53–0·58)
Patient no. 1	0·14 (0·12–0·16)	0·72 (0·70–0·74)	0·84 (0·77–0·88)	0·55 (0·51–0·57)
Patient no. 2	0·14 (0·11–0·18)	0·73 (0·69–0·75)	0·81 (0·75–0·83)	0·56 (0·51–0·59)

The R_f values are compared with those of 5-hydroxytryptophan (5-H.T.P.), 5-hydroxytryptamine (5-H.T.), and 5-hydroxyindoleacetic acid (5-H.I.A.A.) added to normal human urine. Solvent systems: 1. Ascending: isopropanol/ammonia/water (20/1/2). 2. Ascending: butanol/glacial acetic acid/water (12/3/5). 3. Descending: butanol/glacial acetic acid/water (8/2/5). 4. Descending: aqueous KCl (20% w/v).

strated in *Chromobacterium violaceum* (Mitoma et al. 1956) and in the toad venom gland (Udenfriend et al. 1955), direct evidence that this reaction occurs in mammals has been lacking. We have recently seen two patients with malignant carcinoidosis in whom urinary excretion of 5-H.T.P. was demonstrated. In one of these radioactive tryptophan given by mouth was converted to urinary 5-H.T.P.

Urine from 5 patients with malignant carcinoidosis was concentrated by the method of Dalgliesh (1955), and the indolic compounds were separated by paper chromatography (Dalgliesh 1956, Jepson 1955). 5-Hydroxyindole compounds were identified by staining with nitrosonaphthol (Udenfriend et al. 1955). In three of these patients the urine contained only a single nitrosonaphthol-reacting compound with chromatographic properties similar to those of 5-hydroxyindoleacetic acid (5-H.I.A.A.). In the two others, however, three distinctly separate 5-hydroxyindole compounds were demonstrated. In various solvent systems the R_f values of these compounds did not differ from those obtained when 5-H.T.P., 5-hydroxytryptamine (5-H.T.), and 5-H.I.A.A. were added to normal human urine (see table). Moreover, three 5-hydroxyindole compounds with chromatographic properties identical with those of the substances in the urine of these two patients were regularly isolated from the urine of healthy adults who had been given 5-H.T.P. intravenously.

Spectrophotofluorimetric Analysis

Further evidence for the presence of 5-H.T.P. in the urine of these two patients was obtained by spectrophotofluorimetric analysis.

Concentrated urine was applied to Whatman no. 1 paper together with reference samples of pure 5-H.T.P. The chromatogram was developed in butanol/acetic acid/water (8/2/5) and the areas corresponding to the 5-H.T.P. spot were cut out and eluted with water. This eluate was concentrated in vacuo and rechromatographed using isopropanol/ammonia/water (20/1/2). The entire procedure was then repeated a third time using butanol/acetic acid/water. The final eluate was evaporated to dryness and the residue dissolved in either 3*N* or 0·1*N* HCl. Activation and fluorescent spectra of both solutions were analysed in an Aminco-Bowman spectrophotofluorimeter. The curves obtained did not differ from those observed with similar solutions of known 5-H.T.P.

Tracer Studies

Patient 1 was given a single dose of 37·5 μC of DL-tryptophan-2-^{14}C by mouth. A 100 ml. aliquot of the urine collected during the next 24 hours was concentrated, and the 5-hydroxyindole compounds present were purified by chromatography, as described above. Aliquots of the elutions of those areas on the chromatograms corresponding to 5-H.T.P., 5-H.T., and 5-H.I.A.A. were used for spectrophotofluorimetric analysis and for counting in a SC-16 gas-flow counter. The specific activities of the urinary 5-H.T.P. after the second and after the final chromatographic purifications were 93 and 97 c.p.m. per μM respectively. Specific activities of the corresponding 5-H.I.A.A. fractions were 445 and 427 c.p.m. per μM respectively. It is possible that the slow rate of formation of 5-H.T.P. and the rapid rate of its metabolism to 5-H.I.A.A. might account for these differences in specific activities. The amounts of 5-H.T. isolated in this fashion were too small for determination of specific activity.

The presence of 5-H.T.P. in the urine of two patients with malignant carcinoidosis and the demonstrated conversion of ^{14}C-tryptophan to 5-H.T.P.-^{14}C in vivo lend additional support to the concept that 5-H.T.P. is an intermediate in the biosynthesis of serotonin.

We wish to thank Dr. J. B. Jepson for an independent analysis of urine from patient 2 (performed in Dr. S. Udenfriend's laboratory) which confirmed the presence of 5-H.T.P., 5-H.T., and 5-H.I.A.A. This work was supported by grants from the U.S. Public Service, the Miles-Ames Laboratories, and the gastrointestinal fund of the Peter Bent Brigham Hospital.

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THE LIVER IN SCHISTOSOMIASIS

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SINCE the original description by Kartulis (1885), much interest has been focused on changes in the liver associated with schistosomiasis. Granulomatous lesions surrounding the ova were first recognised by Fairley (1919), and have since been described by Koppisch (1941), Bracken et al. (1948), Deschamps et al. (1955), and Ragheb (1956). But the importance and extent of the infiltration of the liver by ova, and the nature and cause of the fibrosis found in the livers of patients with schistosomiasis, are still disputed. The studies of Dimmette (1955), Lichtenberg (1955), and Bogliolo (1957) have thrown light

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on the infiltration of the liver in severe cases, but the extent of liver involvement in clinically mild cases has been little investigated. Following the description of "pipestem" cirrhosis (Symmers 1903, 1905, Day and Ferguson 1909), the concept developed without dispute that schistosomiasis caused hepatic fibrosis. More recently the importance of this fibrosis in relation to cirrhosis has been questioned (Karsner 1943, Hashem 1947) and the view expressed that such fibrosis as occurs may be due to the poor nutritional state of the patients studied rather than to schistosomiasis (Symmers 1951, Mackie et al. 1954).

Most cases studied have been severely infected with schistosomiasis and malnourished, the patients having lived on very poor diets throughout their lives (Dimmette 1955, Ragheb 1956). Schistosomiasis does not seem to have been studied in cases where malnutrition was not conspicuous, except by Latty et al. (1954) and Deschamps et al. (1955), who studied Puerto Rican soldiers on enlistment into the United States Army.

In this paper we present the findings in 36 Nigerian soldiers, all of whom were fit and not malnourished except possibly in infancy. All were clinically mild cases, and were diagnosed by the finding of ova in the urine or stools.

Material

24 cases were of schistosomiasis hæmatobium, 12 of schistosomiasis mansoni, and 2 of mixed infections. The patients' average age was 23 years (range 18–29), their average weight 150 lb. (range 139–181), and their average height 69 in. (range 65–73).

Each man had a medical card dating from the time of enlistment, when no evidence of schistosomiasis was noted. The length of recorded medical attention ranged from 1 to 11 years, with an average of 3 years. The average time from the onset of symptoms (taken in most cases from the record card), to the date of liver biopsy was 14 months, with a range of 1 to 60 months. The majority had had previous courses of treatment.

Urinary cases presented with hæmaturia, usually terminal, and mild dysuria; rectal cases presented with various symptoms including vague abdominal pain and mild diarrhœa, occasionally associated with blood in the stool or tenesmus.

TABLE I—LABORATORY INVESTIGATIONS

—	*Sch. hæmatobium* infections	*Sch. mansoni* infections	Combined cases
No. of cases	22	12	36
Investigation:			
Hæmoglobin (%)	93–112	80–112	
	(101)	*(97)*	*99·5*
E.S.R. (mm. in 1st hr.; Wintrobe):			
Active cases	3–36	24–36	
	(15)	*(30)*	*16*
Inactive „	4–40	1–53	
	(16)	*(15)*	*16*
W.B.C. count	4300–8900	3000–10,450	..
Eosinophils (%):			
Active cases	5–32	30–42	
	(15)	*(36)*	*19*
Inactive „	1–29	0–23	
	(11)	*(10)*	*11*
Serum-protein (g. per 100 ml.):			
Total	5·5–9·0	6·0–9·0	
	(7·4)	*(7·6)*	*7·5*
Albumin	3·1–5·5	3·0–5·2	
	(4·4)	*(4·4)*	*4·4*
Ova in stool at any time	..	13	..
„ urine „ „	22	..	..
Ova in stool at biopsy	..	2	..
„ urine „ „	10	..	..
Ankylostoma duodenale in stool	6	5	11
Ascaris lumbrazoides in stool	7	6	13

Means (arithmetic) are in italics.
The two mixed infections are only included when calculating the means under "combined cases". In neither case did any figure lie outside the ranges quoted.

There was no history of pruritus or rashes before the presenting symptoms. Examination showed the patients to be essentially fit. 7 had a palpable liver, and in 3 of these the spleen was felt also. The liver edge was soft and regular. No other abnormalities were detected. There was no clinical evidence of protein malnutrition, avitaminosis, or pulmonary hypertension. All their chest radiographs were within normal limits.

25% of the rectal cases infected with *Schistosoma mansoni* showed changes on sigmoidoscopy; areas of the mucosa were elevated, hyperæmic, and covered with thick yellow-grey mucus, which on wiping revealed pinpoint hæmorrhages. 50% of the urinary cases infected with *Sch. hæmatobium* showed changes on cystoscopy, ranging from small isolated sandy yellow nodules with occasional ulceration in 8 cases, to frank confluent hæmorrhagic ulceration in 4.

Routine laboratory investigations of all cases included hæmoglobin (oxyhæmoglobin photometrically), total and differential white-blood-cell (W.B.C.) counts, erythrocyte-sedimentation rate (E.S.R.), search for malarial parasites, serum-total-proteins, albumin and globulin, and filterpaper electrophoresis for serum-proteins. The urine and stools were examined for ova, other parasites, pus-cells and red blood-cells. The more important pathological findings are summarised in table I.

TABLE II—RESULTS OF LIVER BIOPSIES

—	*Sch. hæmatobium* infections	*Sch. mansoni* infections	Combined cases
Normal	8	3	11
Abnormal	14	11	25
Ova present:	5	7	12
With reaction	5	3	8
Without reaction	..	4	4
Obsolete granulomata:	7	8	15
With no ova in biopsy	3	4	7
Portal-tract infiltration:	13	12	25
Severe	7	5	12
Slight	6	7	13
Fibrosis:	7	7	14
Conspicuous	3	2	5
Slight	4	5	9
"Hepatitis":	3	2	5
With ova	1	1	2
Obsolete granulomata, without ova	1	1	2

The mixed cases are included under *Sch. mansoni* infections because ova of this species only were found in the liver biopsies.

All patients were treated with one or more of the following drugs: sodium antimony gluconate, sodium antimony tartrate, stibophen, or lucanthone hydrochloride. We gained the impression that sodium antimony tartrate is still the most effective drug for schistosomiasis.

Methods

Liver biopsies were taken with a Vim-Silverman needle, under local anæsthesia, via the intercostal approach in the midaxillary line. Rectal snips were taken with biopsy forceps through a proctoscope. Specimens were fixed in Susa. Liver biopsies were sectioned serially, and rectal biopsies were sectioned at three levels. Sections were stained with hæmatoxylin and eosin (H. & E.), Mallory azan, periodic-acid Schiff, and A. M. Barrett's bone-marrow stain. Most of the work was done with H. & E.

Results

Liver Biopsies (table II)

11 liver biopsies were considered normal, and 25 showed various degrees of abnormality. The changes included ova in 5 cases of *Sch. hæmatobium* and 7 cases of *Sch. mansoni* infection; in the majority the ova were surrounded by a granulomatous reaction, typical of that described by Fairley (1919). A concentric exudate was formed by eosinophils, lymphocytes, plasma-cells, and young fibroblasts, and in many cases the chitinous envelope of the ovum was undergoing digestion by giant cells. In some the body of the miracidium could still be

discerned within the ovum (fig. 1), and the terminal or lateral spines were still distinct, allowing precise species diagnosis. In others the digestion by giant cells had progressed so that only the chitinous envelope remained, and species diagnosis of the ovum was no longer possible (fig. 2).

In some *Sch. mansoni* infections ova were present without surrounding reaction. In 1 the ovum was in a portal-vein radicle, and in others the ova were in the liver parenchyma (fig. 3); similar findings were recorded by Lichtenberg (1955). Some granulomata had small amounts of chitinous material in the centre, and others with no recognisable chitin had a similar structure and appearance. The nature and ætiology of these granulomata were discussed by Deschamps et al. (1955); although they cannot be proved definitely to be of schistosomal origin, they probably represent the end-product of absorption of the ovum by giant cells, with healing by fibrosis. Pigment is often present; these granulomata are referred to in table II as obsolete.

The portal tracts were found to be infiltrated by lymphocytes; in some cases, particularly those with active infection, this was conspicuous, the portal tracts being enlarged and filled by dense aggregations of small lymphoctyes and plasma-cells. There was no definite correlation between portal-tract infiltration and the presence of ova. Where portal-tract infiltration was conspicuous, the small lymphocyte predominated; in some, small numbers of eosinophil and neutrophil leucocytes were present also.

Portal-tract fibrosis was usually apparent as a slight general increase in the size, with mature fibrous tissue.

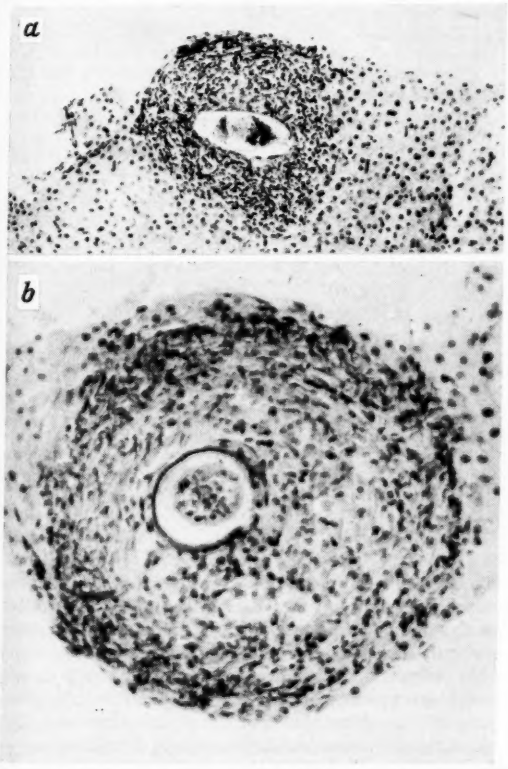

Fig. 1—*Sch. mansoni* ovum in liver with surrounding granuloma: (*a*) H.& E. ×96; (*b*) A. M. Barrett's bone-marrow stain. × 172.

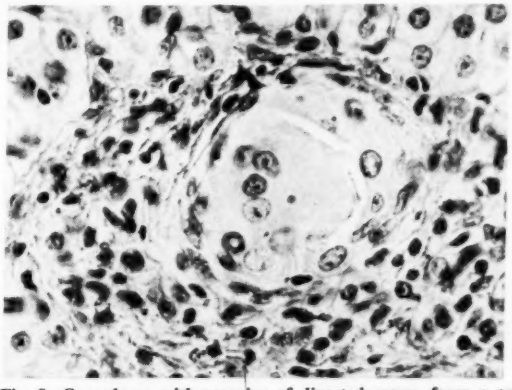

Fig. 2—Granuloma with remains of digested ovum, from a case infested with *Sch. mansoni*. (A. M. Barrett's bone-marrow stain. × 585.)

There was definite correlation between fibrosis and cellular infiltrations; with the exception of new acute cases, fibrosis was always present when infiltration with lymphocytes was conspicuous. Where fibrosis was more severe, the adjacent portal tracts tended to become joined, outlining single lobules, but in 5 cases the fibrosis was rather more irregular, tending to cut into the lobules.

In these 5 cases, the parenchyma was infiltrated by inflammatory cells, again predominantly small lymphocytes and plasma-cells with eosinophil and occasional neutrophil leucocytes. This was always associated with conspicuous portal-tract infiltration with a similar mixture

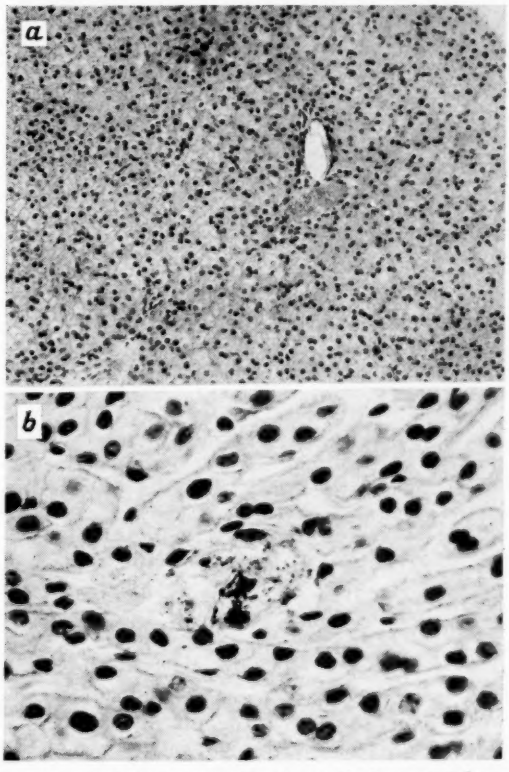

Fig. 3—Ovum of *Sch. mansoni* lying free in the liver parenchyma: (*a*) H.& E. × 96; (*b*) H.& E. × 415.

TABLE III—RESULTS OF RECTAL BIOPSIES

—	*Sch. hæmatobium* infections	*Sch. mansoni* infections	Combined cases
Total no.	21	14	35
Ova present:	13	9	22
With reaction	4	6	10
Without reaction	9	3	12
Cellular infiltration	12	10	22
Fibrosis and irregularity ..	4	5	9

The two mixed infections are included under the *Sch. mansoni* heading.

of cells, and with fairly advanced portal-tract fibrosis in which the portal tracts tended to be linked up so that the fibrosis extended into the lobules, cutting off small groups of cells. This process is technically a hepatitis, the parenchymal cells showing vacuolation, mitoses, and enlargement and irregularity of the nuclei (fig. 4). The finding of 5 such cases with strikingly similar patterns, among 36 cases of mild schistosomiasis, suggests strongly a relation with hepatitis. But the presence of ova did not always correlate with this type of hepatitis; ova were found in 3 of these 5 biopsies, and another showed obsolete granulomata. 3 biopsies were from patients infected with *Sch. hæmatobium*, and 2 from cases infected with *Sch. mansoni*. Neither of the mixed infections showed this feature.

In 5 biopsies wide areas of fibrous tissue, often containing nerves, larger vessels, and bile-ducts, and occasionally obliterated vessels, were found. Their significance is very difficult to assess in aspiration biopsies; they probably represent parts of the hepatic capsule and

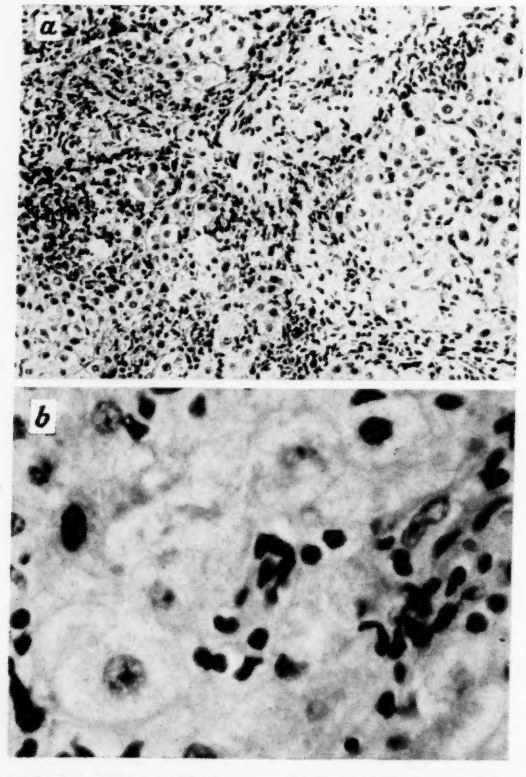

Fig. 4—Liver biopsy with changes of "hepatitis": (*a*) low-power view showing disorganisation of the lobular architecture (H. & E. × 96); (*b*) high-power view showing swollen parenchymal cells and infiltrate (H. & E. × 780.)

ligaments, being disregarded when no ova or other suggestive findings were present.

Rectal Biopsies (table III)

Ova were found much more often, and usually in much greater numbers, in the rectal biopsies. Granulomatous reactions with giant cells were often found in relation to *Sch. mansoni* ova (fig. 5), being present in 5 positive cases and absent in 2; whereas granulomata were absent around ova of *Sch. hæmatobium* in 9 biopsies and present in 3. The reactions took the form of a small syncytium of giant cells surrounding the ovum and digesting it, but without the outer concentric cuff of cells seen in the liver biopsies (fig. 5). A general increase of cells in the lamina propria mucosæ was often found when ova were present, and also

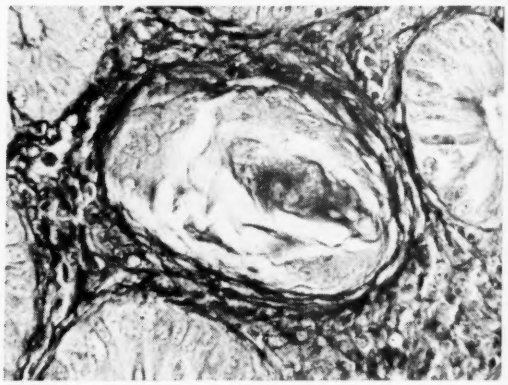

Fig. 5—Ovum of *Sch. mansoni* in rectal mucosa, surrounded by giant-cell reaction. (Azan. × 312.)

There were no cases of infection by *Sch. intercalatum* in this series. The appearance of a double spine is an artefact produced by rotation of the ovum during preparation, leaving a spine-shaped defect in the surrounding syncytium.

in 5 cases where ova were not detected. The cells involved were those normally present in the mucosa—i.e., plasma-cells, small lymphocytes, and eosinophils. Neutrophil leucocytes were never found. 2 cases of *Sch. hæmatobium* infection showed slight fibrosis and scarring; this was moderately conspicuous in 3 infections with *Sch. mansoni* and slight in 2 (fig. 6).

The rectal biopsies showed that the ova of *Sch. mansoni* provoked more reaction and caused more damage than those of *Sch. hæmatobium*. The ova of *Sch. hæmatobium* tended to remain in or near the muscularis mucosæ (fig. 7), whereas those of *Sch. mansoni* were usually at or near the surface of the mucosa itself. The ova of *Sch. hæmatobium* were more numerous in the biopsy sections than those of *Sch. mansoni*. About half the ova of both species were viable as judged by a recognisable miracidium, and only a few were digested.

Discussion

The cases in our series were early; many had been treated previously, and were clinically inactive. All were in good general health, and had probably not been malnourished. The clinical impression of health was supported by the high average hæmoglobin (14·8 g. per 100 ml.) and by the normal serum-albumin levels. But, despite this, we found that 5 of the 36 cases had an active hepatitis, with fibrosis and infiltration of the portal tracts and parenchyma by inflammatory cells, in the absence of icterus or past history of jaundice. The liver was palpable

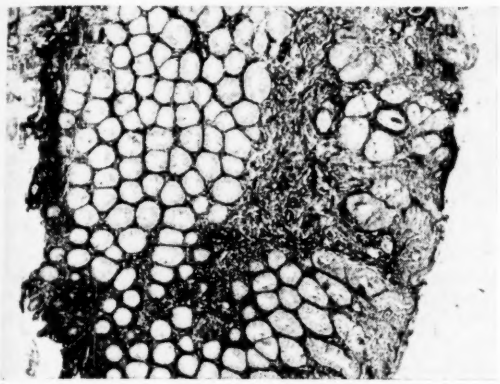

Fig. 6—Rectal biopsy showing fibrosis in relation to numerous ova of *Sch. mansoni*. (Azan. × 33.)

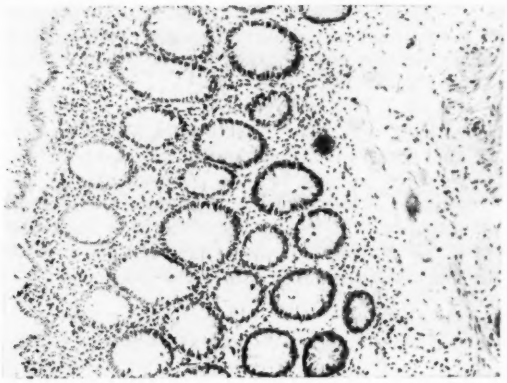

Fig. 7—Rectal biopsy showing numerous ova of *Sch. hæmatobium* in the submucosa. (H. & E. × 72.)

in all 5 and the spleen in 2; their globulin levels as judged by filterpaper electrophoresis were quantitatively greater than in the other cases in the series. 14 cases had some degree of fibrosis in the portal tracts; ova, or remains of ova, were found in 12, and obsolete granulomata in 15. Since an aspiration-biopsy specimen comprises only a very small piece of liver, it is apparent that hepatic involvement in schistosomiasis is extensive even in early and mild cases. Furthermore, infiltration of the portal tracts, which was particularly noticeable in the active cases, suggests that some process more general than the local irritation set up by ova acting as foreign bodies must be at work in schistosomiasis. At the beginning of this study we thought that schistosomiasis caused a diffuse fibrosis, as described by Hashem (1947), without parenchymal infiltration and hepatic-cell damage, and not cirrhosis. But having regard to the above findings, and particularly the active hepatitis in 5 of 36 mild cases, we have had to change our opinion. We now think that schistosomiasis affects the liver in two separate ways.

The first is by the production of small granulomata surrounding the individual ova, which act as foreign bodies. This has little effect on the parenchyma, although the total number of ova and granulomata in any infected liver is likely to be large, as judged by these small biopsy specimens. Dimmette (1955) showed that more positives were found in wedge biopsies taken at laparotomy, and that the number of positives was increased by taking two aspiration biopsy specimens. If our biopsies had been repeated, we think that ova would have been found in more cases. The only major pathological effect of the ova themselves seemed to be " pipestem " cirrhosis, possibly arising as a fibrosis surrounding the main portal veins because of the large numbers of ova in the perivenular tissue in heavy infections. This fibrosis strangles the veins and leads to portal hypertension. No such cases were found in our series, but this is not surprising as it seems to be essentially associated with heavy infections.

The second mode of attack is more obscure. There is a general increase in inflammatory cells in the portal tracts, leading ultimately to the development of mature fibrous tissue. In certain cases with a more pleomorphic cellular infiltrate, not only the portal tracts but also the sinusoids and the substance of the lobules are infiltrated in association with diffuse perilobular fibrosis and parenchymal-cell disturbance. No definite proof exists that this is schistosomal in origin; but since so many workers have observed it (Deschamps et al. 1955, Dimmette 1955, Ragheb 1956), and since it was conspicuous even in our mild cases, we think it should be regarded as schistosomal hepatitis unless this can be disproved. Whether schistosomal hepatitis progresses to cirrhosis cannot be decided from our studies; but the activity of the lesions was such that we think they must lead to irreversible liver damage in some cases.

Certain other points have emerged from our study. One previously stressed only by Ragheb (1956) is the importance of *Sch. hæmatobium* in causing liver pathology. The 14 abnormal liver biopsies in the cases infected with *Sch. hæmatobium* included 3 of hepatitis and 5 in which there were ova. Most reported hepatic lesions have been in *Sch. japonicum* or *Sch. mansoni* infections, but our studies show that *Sch. hæmatobium*, although less virulent, can also cause liver damage. Another observation concerns the relative frequency of the two species of schistosoma in Nigeria; most physicians working there think that *Sch. hæmatobium* infections account for almost all schistosomiasis, and Okpala (1957) found a ratio of 39/1 for *Sch. hæmatobium*/*Sch. mansoni* in routine stool and urine analysis over 4 years. But *Sch. mansoni* infections, which formed 40% of this series, seem to be fairly common in Army practice.

Rectal biopsies show that the irritation and fibrosis produced by *Sch. mansoni* are different from those caused by *Sch. hæmatobium*, and that the strictures seen macroscopically in *Sch. mansoni* infections must be related to the greater irritation produced by these ova, or to the difference in their distribution. This may be a mechanical feature, the lateral spine of the *Sch. mansoni* ovum enabling it to penetrate the mucosa more easily. It may also account for the extreme scarcity of *Sch. hæmatobium* ova in the stools compared with *Sch. mansoni* ova, although we have often seen large numbers of *Sch. hæmatobium* ova in rectal biopsies.

In diagnosis rectal biopsy is an extremely useful adjunct to the routine search for ova in stools and urine, being a simple procedure, which when properly carried out causes no discomfort, and should not be followed by complications. The biopsy specimen need not be examined histologically as we have done for research purposes; normally it suffices to digest the specimen and examine the centrifuged deposit for ova. Liver biopsy as a diagnostic procedure is different; the number of ova in relation to the volume of tissue, and the non-specific nature of any

other findings, render its value small. In our series ova were never found in the liver when they were not in the rectum; and this may be related to the route by which ova arrive in the liver.

Summary

Liver biopsies were performed on 36 Nigerian soldiers with mild schistosomal infections in an attempt to assess the extent and severity of liver involvement.

Two types of liver damage were recognised: granulomata produced by ova acting as foreign bodies; and hepatitis progressing to diffuse fibrosis, unrelated to ova.

We wish to thank Mr. E. W. Kent for the photomicrographs.

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EOSINOPHIL LEUCOCYTES IN ULCERATIVE COLITIS

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THE eosinophil leucocyte has been little studied in relation to ulcerative colitis.

Machella and Hollan (1950) are the only workers to report figures for eosinophil leucocytes in the blood, and their series consists of only three patients with ulcerative colitis. Of these patients, there was pronounced blood eosinophilia at the time of relapse in one, while the other two had mild eosinophilia. These and other workers (Kirsner and Palmer 1954) were chiefly concerned with the fall in blood-eosinophils occasioned by corticosteroid therapy.

If blood-eosinophilia were found to occur regularly in attacks of ulcerative colitis, this would have a bearing on the ætiology of the disease. The present study deals with the blood-eosinophil count in a group of patients with ulcerative colitis attending a special clinic for treatment and supervision. The objective was to determine the blood-eosinophil count in patients with a relapse judged clinically, and to compare it with the count in patients free from symptoms. It was also hoped that, by making serial studies on selected patients, the eosinophil count could be related to frank clinical relapse.

Material and Methods

The patients were chosen from adults of both sexes with a history of relatively frequent relapses in which there was diarrhœa as well as the passage of blood and mucus. Mild cases, in which there was occasional passage of blood per rectum, but no diarrhœa, were not studied. Fulminating attacks progressing into severe dehydration and anæmia were likewise excluded.

Eosinophil counts were done on blood taken from twelve patients in remission, all of whom had had at least two previous attacks of ulcerative colitis, but in whom the last three months had been symptom-free. None had received any form of corticosteroid therapy for two months. Cases 1 and 12 had earlier been investigated during periods of relapse.

BLOOD-EOSINOPHIL COUNT IN ULCERATIVE COLITIS: IN 12 PATIENTS IN REMISSION, AND IN 12 PATIENTS IN CLINICAL RELAPSE

During remission				During relapse			
Case no.	Sex	Age (yr.)	Eosinophil count (per c.mm.)	Case no.	Sex	Age (yr.)	Eosinophil count (per c.mm.)
1	F	31	180	1	F	31	80
2	M	47	94	13	M	28	212
3	F	45	120	14	F	48	306
4	M	30	190	15	F	47	420
5	M	30	170	16	M	47	230
6	M	46	120	4	M	30	440
7	F	32	110	5	M	30	247
8	F	26	181	7	F	32	331
9	M	38	100	17	M	43	170
10	F	44	70	12	M	39	150
11	F	24	76	18	M	46	600
12	M	39	110	19	F	28	660
Mean			127				320

Significance of difference between the two samples: t = 3·85; for 22 degrees of freedom, P = 0·001.

Counts were made on 12 patients in clinical relapse, before, and during, corticosteroid therapy. Cases 4, 5 and 7 were investigated as they proceeded from remission into relapse. All 12 had had previous attacks, during some of which they had been treated with corticosteroids, except case 13 in whom the presenting attack was the first treated in this manner.

All the observations reported were made in eight consecutive months.

Technical Methods

Blood was taken by venepuncture, collected in a "heparinised" tube, and agitated for two minutes, and again just before sampling by a white-blood-cell pipette. Eosinophil counts were made according to the method of Dunger (1910), using eosin-acetone-water as diluent, two separate pipettes being employed to fill the chambers of each of two Fuchs-Rosenthal slides. Total counts were made, the whole procedure being completed within an hour of the collection of the blood, to prevent "clumping" of the eosinophils.

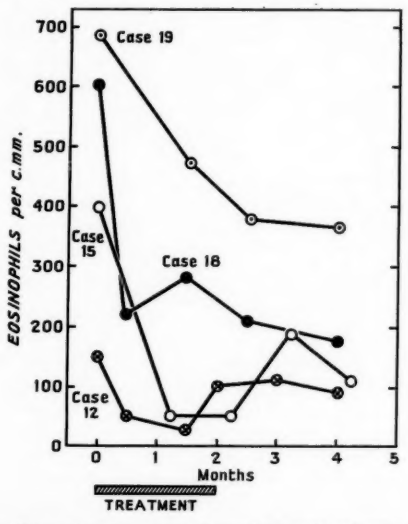

Fig. 1—Effect of various types of corticosteroid therapy on blood-eosinophil count of patients with ulcerative colitis.

Case 19: Oral triamcinolone plus rectal drip of hydrocortisone hemisuccinate-sodium.
Case 18: Prednisolone phosphate by rectal drip.
Case 15: Oral prednisolone.
Case 12: Oral prednisolone plus rectal drip of prednisolone phosphate.

The experimental error is ±10 when 100 cells are counted, proportionately greater accuracy being achieved as more are estimated (Dacie 1956). The normal range of values was taken as 60–200 cells per c.mm. (Hills et al. 1948).

Results

The accompanying table shows the blood-eosinophil counts recorded in patients in remission and relapse. The constitution of the two groups was closely similar in respect of age and sex. The twelve patients in clinical remission had a mean blood-eosinophil level of 127 per c.mm. No patient who was symptom-free had a count higher than 200 per c.mm. The mean blood-eosinophil level in the twelve patients during clinical relapse was 320 per c.mm.; nine of the values recorded were above 200 per c.mm. The difference between the two samples is statistically significant.

Response to Successful Therapy

Corticosteroids can be administered both systemically and topically in ulcerative colitis. When a suitable combination of these drugs was given by one or both routes, improvement, judged clinically and by sigmoidoscopy, was evident in each case. Simultaneously, the blood-eosinophil count fell below the figure found at the beginning of relapse. If therapy was not effective, the eosinophil count continued to rise until adequate corticosteroid therapy was instituted (see fig. 2, case 4). Examples of the effect of various combinations on the eosinophil count are shown in fig. 1.

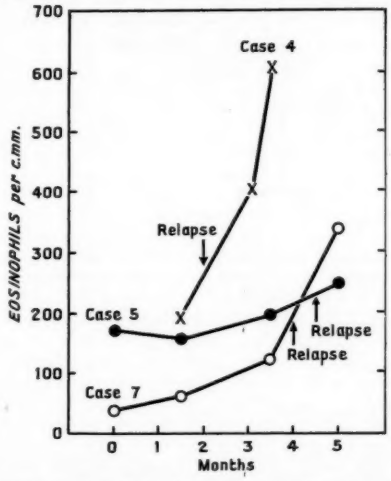

Fig. 2—Blood-eosinophil levels in patients with ulcerative colitis passing from remission to relapse.

In all twelve patients circulating eosinophils decreased when effective corticosteroid therapy was introduced.

Changes with Clinical Relapse

Chance governed the number of patients caught between remission and relapse. Two patients who each had had two counts made whilst in remission had a significant rise in their blood-eosinophil levels before clinical signs of relapse appeared (fig. 2). In each case, clinical symptoms appeared at a time when the eosinophil count rose above the upper limit of the " normal " range. By contrast, two patients on whom counts were made over a minimum period of five months, and in whom no signs had developed, showed no rise in their eosinophil levels (fig. 3). In a third patient who had passed from remission into relapse (fig. 2, case 4), only one count had been performed before symptoms appeared. At this count he was found to have 190 cells per c.mm., which was the highest count in the twelve patients in remission. Subsequently, his blood-eosinophil count rose even higher before effective treatment was instituted.

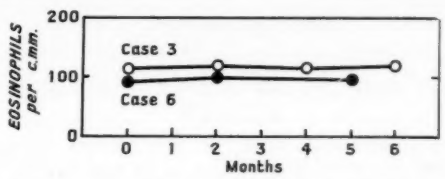

Fig. 3—Blood-eosinophil levels in two cases of ulcerative colitis in remission, without corticosteroid therapy.

Discussion

The number of eosinophils circulating in the blood is known to depend on the functional activity of the adrenal cortex, being lowered in Cushing's syndrome and raised in Addison's disease (Thorn 1948, Hills et al. 1948). The eosinophil count is consistently raised by exposure to antigens (Vaughn 1953, Spiers 1955); indeed Ringoen (1938) stated that eosinophilia is a constant and definite feature of allergy.

The ability of various drugs to relieve allergic disorders, considered with their effect on blood-eosinophil levels, further suggests that this cell has a significant role in this group of diseases. Anti-histamine drugs, given before exposure to an antigen, partly prevent the formation of urticarial wheals, angioneurotic œdema, and hay-fever. They will not prevent asthmatic attacks, nor will they relieve ulcerative colitis (Kiefer 1948); nor do they affect the blood-eosinophil level. In contrast, adrenocorticoids in sufficient dosage will much improve the allergic disorders that have been mentioned, as well as ulcerative colitis. These drugs cause a fall in the number of eosinophil leucocytes circulating in the peripheral blood.

The rise in eosinophils attendant on relapse, described here, is a feature that ulcerative colitis shares with allergic conditions of the respiratory tract and the skin. Further investigation of this relationship would be of value in elucidating the ætiology of ulcerative colitis.

Summary

In each of twelve patients with ulcerative colitis in remission the eosinophil count was normal; whereas of twelve patients with ulcerative colitis in relapse, nine had eosinophilia.

Serial counts during passage from remission to relapse showed that a rise in the eosinophil count preceded the onset of symptoms.

Treatment of an attack of ulcerative colitis by corticosteroid therapy is accompanied by loss of eosinophilia only when the treatment proves effective.

I am grateful to Dr. S. C. Truelove for his permission and encouragement to make this study on patients in his care, and for his helpful criticism.

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Medical Society

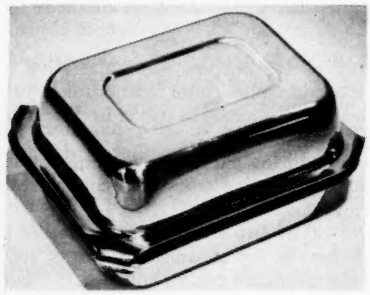
DEVON AND EXETER MEDICO-CHIRURGICAL SOCIETY

AT a meeting on Nov. 19 Dr. JACK SIMPSON discussed dementia and confusional states in the elderly. It was important, he said, to recognise that these were separate and distinct. Dementia was a slowly progressive disintegration of intellect and personality. In such cases there was often a crust of normality or, at any rate, there were intervals of apparent normality; but the condition was characterised by forgetfulness and dissociation and might proceed to hallucinations or delusions. In confusional states, on the other hand, the onset was often abrupt. There was evidence of underlying social, psychic, or organic illness, and the patient might be agitated, aggressive, or apathetic. Among the ætiological factors were environmental disturbances, emotional upsets, psychoneuroses, drug-addiction (notably to bromides and barbiturates), malnutrition, myxœdema or thyrotoxicosis, anoxia from any cause, and various toxic states. The diagnosis having been established, bed rest should be limited and the aim should be to restore normal activity rapidly. Activity by day conduced to sound sleep by night. Parenteral vitamin B was of value, but sedatives should be used sparingly. Thalidomide or glutethamide at night was often all that was necessary. If these failed chlorpromazine with promethazine was a useful combination, and, in the last resort, paraldehyde should be used.

New Inventions

GUY'S HOSPITAL INSTRUMENT TRAY

THIS stainless-steel instrument tray was produced as a container of sterile sets for ward procedures such as dressing, aspiration, and catheterisation. The kidney dishes commonly used have various disadvantages: their shape is obsolete; their curled edges are difficult to clean; and when they are used as top and bottom, the top one slips off. All these objections



are overcome by this instrument tray. It has a straight flange, curled slightly up and down at alternate corners to prevent sliding apart; the top and bottom are identical and fit correctly either way round; and they stack compactly without jamming, for storage or sterilisation.

The tray was devised ten years ago in the Department of Surgery, Guy's Hospital, with the assistance of the Metal Box Company, and has proved very satisfactory. It is made in two standard sizes (approximately 8 × 6 in. and 10 × 8 in., by The Taw Manufacturing Co. Ltd., Hornsey, London, N.8.

Department of Surgery,
Guy's Hospital,
S.E.1.

REX LAWRIE
M.S. Lond., F.R.C.S.

CONTROL UNIT FOR BLOOD-PRESSURE RECORDING

DURING many procedures in surgery, and during cardiac catheterisation, it is often desirable to make continuous recordings of intravascular pressures. Such recordings should be capable of running unattended for several hours.

The instrument described here allows a slow continuous intravascular infusion of saline to be automatically maintained

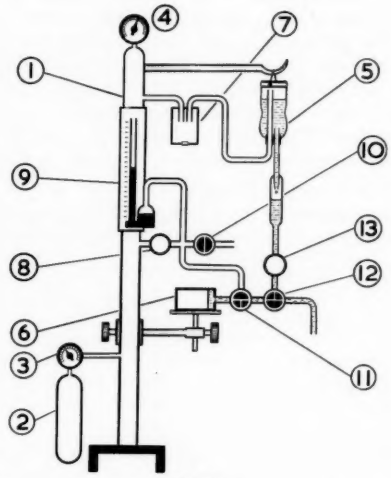


Fig. 1.

along the catheter or intra-arterial needle through which the blood-pressure is recorded. It also provides standard pressures for calibrating a transducer.

The control unit is in the form of a transfusion stand, shown diagrammatically in fig. 1. The central column (1) is a tube 6 ft. long and $1^3/_4$ in. in diameter, which acts as a pressure reservoir. It is supplied by an oxygen cylinder (2) fitted with an Adams regulator (3). The set screw of the regulator allows the pressure in the column to be adjusted between 150 and 400 mm. Hg, and the actual value is read on the gauge (4).

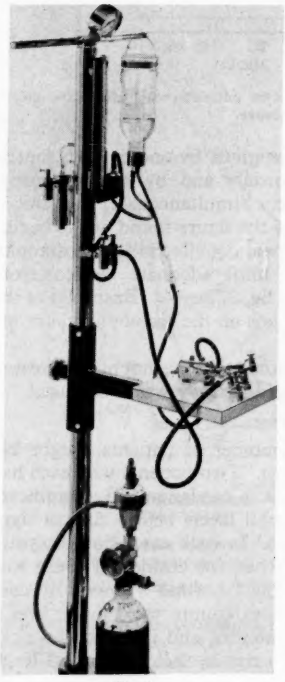


Fig. 2.

The reservoir column is used (a) to pressurise a transfusion bottle (5) and (b) to provide a calibrating pressure for the transducer (6).

The bottle is supplied via a liquid trap (7) which prevents saline drops from entering the column. The calibrating pressure is controlled via a needle valve (8) and is read on a mercury manometer (9) mounted on the column. Tap (10) restores the calibrating pressure to zero.

The transducer unit is carried by an arm mounted on the column, and may be adjusted for height to allow "zero pressure" to correspond to any level on the patient—e.g., the level of the sternal angle. The transducer is fitted with

three-way taps (11 and 12). The pressurised drip system is applied via (12) and adjusted for rate by means of a small needle valve (13). The calibrating pressure can be applied as required via tap (11) without interrupting the flow of saline through the catheter or needle. In this way clotting is prevented. The taps are designed with stops to prevent incorrect connections. For example, the calibrating pressure cannot be connected to the catheter. In addition the plug portion of the tap is held by a spring into the body so that any wear is automatically taken up and leaks cannot occur.

During recording the drip-rate is set for maximal flow, which does not appreciably alter the pressure being measured. For example, using a no. 7 cardiac catheter for venous pressure a suitable rate is about 4 drops a minute.

Any suitable transducer such as an inductance, resistance, or capacitance type may be used with the blood-pressure stand. The complete stand is shown in fig. 2.

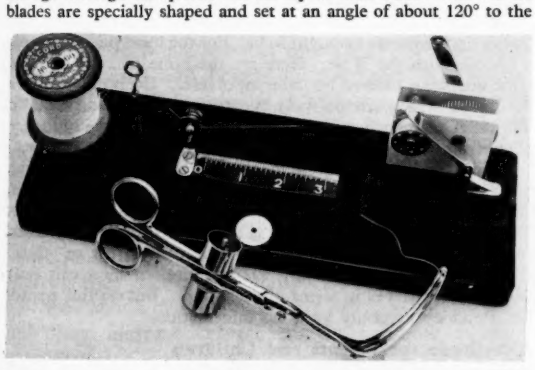
This instrument has been used without failure two or three times a week during the past two years, and is now manufactured by Southern Instruments Ltd., and marketed by Siemens Edison Swan Ltd.

Westminster Children's Hospital, S.W.1 P. CLIFFE M.B., PH.D. Lond., B.SC. Wales

CONTINUOUS-FEED DOUBLE-LIGATURE CARRIER AND TISSUE-SPREADER

EVERY surgeon seeks to simplify as far as possible the common manœuvre of doubly ligating and dividing a vessel or a segment of vascular tissue, and various ligature carriers have been designed to meet this need. The instrument illustrated here has additional advantages over those at present in use in acting as a tissue-spreader and in providing two ligatures which may be of a different gauge.

The reel cases are attached to the sides of each handle, and the reels are held in position for unwinding by screw on lids. The reels hold up to 50 yards of 40 or 60 linen thread. Each ligature emerges from a slot in the reel case and passes through an aperture at the base of the distal or moving blade. The ligatures then separate and pass into their respective grooves on the inner aspect of each blade, where they are held in position by three small bridges, and finally emerge through an aperture at the tip of each blade. The curved blades are specially shaped and set at an angle of about 120° to the



handles for ease in the supination-pronation manœuvre. Wide separation between the movable distal blade and the proximal fixed blade is effected by an amplifying mechanism at the joints. The instrument has advantages over the Cleveland type of ligature carrier quite apart from the continuous-feed ligature attachment, and may be used in this way.

It is helpful to the nursing staff to have a simple apparatus, such as that illustrated, for winding the reels evenly and quickly. It is convenient also to have several reels which have been wound and autoclaved ready for reloading during the operating list. The ligature material should never be boiled. The ligature carrier, like all surgical instruments with moving parts, should be treated at least twice a week with a sterilising oil such as AC.10. (Down Bros.).

The ligature carrier and the reel winder have been made for me by Murphy Boyle, Ltd., 69, Wimpole Street, London, W.1.

Whipps Cross Hospital, London, E.11 D. LANG STEVENSON F.R.C.S.E.

Reviews of Books

The Child with Abdominal Pains

JOHN APLEY, M.D., F.R.C.P., consultant pædiatrician, United Bristol Hospitals. Oxford: Blackwell Scientific Publications. 1959. Pp. 93. 12*s*. 6*d*.

RECURRENT abdominal pain in childhood is one of the commonest and most difficult problems for general practitioners and pædiatricians. This small book, by a pædiatrician with much clinical experience who has studied the subject intensively for many years, presents the data from a large controlled investigation in Bristol. The first half is devoted to the Bristol survey and the second to a discussion of the causes, diagnosis, and management of the child with recurrent abdominal pain.

There was an incidence of 11% in unselected children and a high incidence of abdominal pain, peptic ulcer, headache, and "nervous breakdown" in the relatives of affected children. The children themselves showed increased liability to headaches and bilious attacks. Moreover, a high proportion of young adults who had attended hospital with recurrent abdominal pain in childhood were found to have continuing symptoms, nearly half of them having nervous disorders; a third continued to have attacks of abdominal pain (nearly always with other symptoms), and in a third abdominal pains ceased but other symptoms developed, notably recurrent headaches which were sometimes migrainous. Only a third were symptom-free.

Organic causes of the pain were found in only 8% of those extensively investigated, and a causal relationship with epilepsy could rarely be demonstrated. Compared with controls, children with recurrent abdominal pain tended to show characteristic personality traits, and expressions of emotional disturbance were much commoner. Since the majority of abdominal pains were psychogenic it is not surprising that "informal psychotherapy" was much the most successful form of treatment. The author's advice about the attitude towards these children and their parents is most understanding and very sound, as exemplified by his advice that "effective treatment starts with the first words spoken at the first consultation" and "the more time the doctor spends on the history, the less time he is likely to spend on treatment". This is a really practical and helpful book.

David Livingstone

Family Letters 1841–1856. Editor: I. SCHAPERA, D.SC. London: Chatto & Windus. 1959. In two volumes. Pp. 266 and 320. 60*s*. the set.

THE editor of this collection of Livingstone's letters is professor of social anthropology in the University of London and the author of several standard works on the native tribes of Central Africa. These two volumes contain some 115 letters written by Livingstone between the time he first left England and the year in which he finished his work in Bechuanaland and, acclaimed as a great explorer, returned home to plan his Zambesi expedition.

The collection derives chiefly from letters to his parents, wife, and father-in-law, and is of interest as throwing considerable light on Livingstone's character during this important first period of missionary work. It is easy to see that, far from being by nature a recluse, he felt keenly the separation from his family; and it is a little surprising to discover that his relations with some, at any rate, of his fellow missionaries were far from cordial. Another notable point that emerges is that the charge that he supplied arms to the natives, so often levelled against him by the Boers, and firmly repudiated, had, in fact, a real basis even if the number of weapons involved was only small.

For a medical reader the most interesting passages are the almost laconic ones in which Livingstone describes how a lion inflicted a compound fracture of his humerus, and those in which he prescribes at a distance for the ailments of his relations. And a brief reminder of just one of the tribulations he had to undergo is provided by the account of how his wife, completely untrained in such things, extracted, under his direction, one of his teeth.

Infant Mortality in India 1901–55

S. CHANDRASEKHAR, director, Indian Institute for Population Studies, Madras. London: Allen & Unwin. 1959. Pp. 175. 20*s*.

THE title of this good and delightfully written monograph is too modest; for the book includes not only a study of infant-mortality rates but of registration, census-taking, and the accumulation and analysis of vital statistics in a developing area, and much of it applies to all ages.

In fact it is a pity that so much attention has been given to the infant-mortality rate, and so little to other ages. Everywhere in the world it is found that (*a*) the younger the child at death, the less likely is either the birth or death to be registered, so that a slightly older group is more likely to repay study; and (*b*) the greater the distance from the registration centre, the less accurate are the statistics. Yet the author does not take the opportunity of comparing urban and rural figures. Prof. F. A. E. Crew pointed out [1] that the deaths under 5 years are 5% of the total deaths in Sweden, but nearly 50% in Mexico, and this is a useful method of comparison.

The author specifies data needed to determine the size and the causes of infant mortality. He omits to mention " by whom delivery conducted ". It would be interesting to compare the infant-mortality rate in a place like Bombay, where 70% of the births are said to take place in hospitals, with figures from other areas. The author appreciates the fact that a reduced infant-mortality rate goes hand in hand with a reduced birth-rate. But it is only when good parental responsibility has been developed that most people are able consistently to adopt the techniques of family planning.

While statistics are a valuable aid to medical policy, they are only reliable where there is a good and comprehensive medical service: one does not go without the other.

Scenes from Institutional Life

JOHN VAIZEY. London: Faber & Faber. 1959. Pp. 109. 10*s*. 6*d*.

THIS is a grim piece of autobiography, raising large questions. In 1943 the author, then a schoolboy of 14, was struck down suddenly by acute osteomyelitis of his right ilium (or thereabouts) and found himself forthwith in an adult male ward of a county council hospital, seemingly not far different from the Poor Law Infirmary it had probably once been. It was, of course, a black war year and penicillin was not yet. He nearly died and suffered severely in body and spirit. His account, clearly factual, spares no-one, himself included. He was transferred, in a closed plaster, to a long-stay country children's hospital where surgical, nursing, and educational care were very much better but imaginative kindness " patchy "; and when flying bombs came, this hospital, but without the sister he found the best, was evacuated to some remote spot, where he very slowly recovered in body but continued seared in soul. He finally left hospital, intellectually established, and within sight of physical rehabilitation, after nearly two years of it, aged 16. Now he " looks back in anger " and has very hard words for institutions.

The book will make painful and thought-provoking reading for doctors and nurses whether in institutions or outside. Some, sharing the author's make-up and outlook, will go all the way with him, others not nearly so far. We may hope that, on the whole, hospitals have improved in efficiency and humanity since 1943.

Somatic Complications Following Legal Abortion

JAN LINDAHL, department of women's diseases, Karolinska Institute, Stockholm, Sweden. Oslo: J. W. Cappelers Forlag. London: Heinemann Medical Books. 1959. Pp. 182. 42*s*.

IN certain years since 1946, as many as 5% of all pregnancies in Sweden have been terminated by legal abortion. In view of the extent of the practice it is not surprising to learn that the Swedish Medical Research Council have stimulated and encouraged an investigation into the late effects of termination of pregnancy. Martin Ekblad has already given his account [2] of the results of a psychiatric follow-up examination of 479 Swedish women who had been granted legal abortion on psychiatric grounds. Dr. Lindahl, writing also from the Karolinska Institute in Stockholm, has here set down his findings in regard to the physical complications which have followed therapeutic abortion. The two books are complementary.

Dr. Lindahl analyses 1188 cases of legal abortion which were performed in six departments of gynæcology in Stockholm between April, 1952, and May, 1953. Many different surgeons performed the original operations, but Dr. Lindahl was able, personally, to question and examine 1013 of the women between one and five years after operation. The indications for termination and the surgical techniques used differ greatly from current practice in this country. Quite apart from the wider sociomedical, ethical, and humanitarian reasons which are accepted as grounds for legal abortion, there were, in this large review, surprisingly few operations for sterilisation (144 out of 1188 cases). The commonest operation was vaginal hysterotomy. Very few pregnancies were terminated by dilatation and curettage or abdominal hysterotomy. Perforation of the uterus, intestinal obstruction hæmorrhage requiring blood-transfusion, pelvic inflammatory disease, thrombosis, and hæmaturia were regarded as serious immediate complications in 3·6% of cases. In the long-term follow-up, endometriosis in the vaginal hysterotomy scar was the most important complication. There appeared to be little risk of permanent impairment of fertility after therapeutic abortion, nor was there evidence to show that subsequent pregnancies were more liable to complication.

Read in conjunction with Ekblad's monograph, this book gives an admirable account of the consequences of therapeutic abortion in Sweden today.

Notes of a Soviet Doctor

2nd ed. G. S. PONDOEV, honored physician, Georgian S.S.R. New York: Consultants Bureau. London: Chapman & Hall. 1959. Pp. 238. 40*s*.

THIS small book deals with the sort of subject that is commonly chosen for lectures at the opening of medical schools and for other ceremonial occasions: The Vocation of the Doctor, Medicine—Art or Science?, The Doctor and Patient! It provides an excellent opportunity of finding out what the Soviet doctor thinks he ought to be. For the most part he shares his ideals with the West. Here are the same maxims and the same warnings, uttered by different oracles. Even the jokes are the same (" the operation was a success but the patient died "). The chief difference is in the great weight given to the influence of environment and to psychosomatics derived from Pavlov.

The book is coloured by ideological thought. Everything must be derived from or reconciled with dialectical materialism, and the sanctity of dogma is almost medieval. The Soviet doctor sees the way of truth but is surrounded by darkest error. It would be interesting to know whether this is just an official cliché or whether, as in any age of religion, men can only describe themselves in terms of their faith. But on this matter Dr. Pondoev naturally gives no information.

Anæsthesia for Infants and Children

ROBERT M. SMITH, M.D., anesthesiologist, The Children's Medical Center, Boston, Mass., assistant clinical professor of anesthesia, Harvard Medical School St. Louis: C. V. Mosby. London: Henry Kimpton. 1959. Pp. 418. 90*s*.

FOR most doctors anæsthesia for children almost begins and ends with giving an anæsthetic for the removal of tonsils and adenoids, and only a few are called upon to deal with the varied difficulties which arise when anæsthetia is required in neonatal life or infancy. Yet the physiological and pharmacological problems set by such small patients, though similar in fundamentals to those of adults, require not only greater exactitude in their handling but also an intimate knowledge of those alterations conditioned by age, malformation, or disease, if the final outcome is to be consistently successful and free from complications. All these facets, and many others, are dealt with in this well-written work. Dr. Smith provides a fascinating and instructive study which is very well illustrated and likely to remain a work of reference for many years to come.

1. *East Afr. med. J.* 1957, **34**, 487.
2. Ekblad, M. *Acta psychiat. neurol. scand.* suppl. 99.

THE LANCET

LONDON 5 DECEMBER 1959

The Price of Planning

CURRENT political thought takes planning for granted: opinions differ only on where the division between the planned and unplanned areas of social activity ought to be made. Hence we are in some danger of becoming blind to the limitations of planning and of failing to recognise that some of the troubles of the National Health Service, for example, are the result of these limitations and not of the stupidity, obstructionism, or malice of this or that Government department or professional group.

In an epilogue to his book on *The English Health Service* [1] Professor ECKSTEIN gives some of the reasons why perfectly rational planning cannot be expected—notably, the psychological difficulty of the decisions which the planners have to make, the pressures to which they are subjected, and their lack of control over a multitude of factors crucial to adequate calculation. Even purely financial limitations mean that the decision to install a maternity wing in hospital A may imply a decision not to improve the kitchen in hospital C or to build a new X-ray room in hospital D, and so on. To make such choices rational would require omniscience; and how is the planner, doing his best with data which by no means match his responsibilities, to feel happy in solving such human problems as whether a given sum should be used for the treatment of cancer or of mental illness, and in Manchester or in Bristol? (For regional hospital boards and boards of governors of teaching hospitals, these difficulties, as ECKSTEIN points out, are in practice intensified by a system of Treasury control which deprives them of flexibility in handling their money.) Knowing that completely rational planning is impossible, authorities seek ways of escape: they impose uniformity, which eliminates individual considerations; they base decisions on political acceptability; they perpetuate temporary expedients; they postpone action pending indefinite research and inquiry; and they increase central control. These familiar administrative dodges are characterised by ECKSTEIN as the substitution of non-rational modes of behaviour for rational planning; but they are often all too rational modes of evading awkward decisions.

It is illuminating to apply ECKSTEIN's remarks to some current Health Service issues. What has become known as the senior-registrar problem is both wider and deeper than its name implies. The number of senior registrars established in 1948 was in theory related actuarially to the expectation of consultant vacancies, because senior registrars were to be regarded as consultant trainees. The inflation of their number, which for various reasons soon took place, disturbed this delicate ratio; and irrational considerations (to use ECKSTEIN's term) have so far made the problem insoluble. The financial parsimony of successive Governments towards the Health Service induced in consultants a not altogether irrational fear that any new grade in the hospital establishment would be used for saving money on consultants. The resulting trench warfare on this subject between the Joint Consultants Committee and the Ministry of Health lasted for seven years before reason called a truce. The present structure of hospital staffing in the Health Service, set up in 1948, was based on that which existed in 1939; yet, after twenty years of the most rapid advances in the history of medicine, the Ministries and the medical profession have only just begun to cooperate in a working party to find out what sort of structure is appropriate to the needs of today. And even if the working party succeeds in answering this question, its time will have been wasted unless both the Government and the profession are prepared, having willed the means, to will the end also, and do what it recommends.

Trench warfare is also a fair description of the "negotiations" carried on in Whitley Committee B, which deals with the remuneration of hospital medical staffs. A less rational method of settling such questions can hardly be imagined. Whitley councils were originally devised, during the first world war, to facilitate negotiations between the management and the workers in industry. But in industry each party is a free agent and each has its own weapons which, if necessary, it can use to enforce its opinion. Whitley Committee B is an attempt to transfer the machinery of industrial relations to a profession wholly unfamiliar with such methods and naturally averse to the use of industrial weapons. Moreover, though the doctors are free agents, the "management side" is little more than a mouthpiece for the Treasury; and, because either side can veto an appeal to arbitration, unresolved disputes can end only in stalemate. It is much to be hoped that the Royal Commission will manage to improve on this. In a laissez-faire system disputes tend to be limited and brief, soon settled by the parties on a basis of compromise or by the victory of one or the other. But the introduction of the State as a planner encourages indefinite procrastination, since, whether the State is itself a party to a dispute or is merely holding the ring for the combatants, it seeks to postpone as long as possible a decision which is bound to be unpopular with one or other side, and perhaps both. Hence the years of dispute over the doctors' pay, where perhaps the significant thing is not how little the State has conceded but the fact that it has slowly been forced to retreat. The dispute about the registration of the professions "supplementary to medicine" is another example of the phoney war. Here for years the Ministers have used all the tactics of committees, conferences, and delays to avoid having to offend either the doctors, who want effective control over the training and registration of these other professions, or the professions themselves, which demand autonomy. Perhaps the Government

1. The English Health Service. By HARRY ECKSTEIN. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959. See *Lancet*, Sept. 12, 1959, p. 338.

would argue that only time will accustom people to the inevitable compromise, and that their new Bill will be acceptable now whereas it would have been unacceptable before. But more important, we should say, is the fact that attempts to combine the methods of laissez-faire with those of planning encourage the refusal both to make decisions and to accept them.

More subtle but no less serious dangers arise from recourse to uniformity. One of the great advantages of a laissez-faire system is freedom to experiment. Something fresh, such as a new kind of specialist department in a hospital, or a new grade of assistant, can be tried initially on a small scale. If it fails, little harm is done: if it succeeds it will be copied. But how can such experiments be introduced into a system based on national uniformity which can be changed only after long and cumbersome inquiry and debate, and then must be changed everywhere? At a time of rapid evolution in medicine, mutation is the raw material of advance. Are we in danger of substituting the dinosaurian State for the smaller but more adaptable and progressive mammal?

ECKSTEIN's final point is that "the villain, if there is one, is neither *laissez faire* nor planning, but perfectionism". We expect too much of our planners, and when we fail to get it we either ask for more and better planning (like Erythro on p. 1025) or (like Eryximachus) blame the system. Yet we must have planning, and in the Health Service its achievements are great and obvious. We may achieve more if we expect less, by recognising the limitations of planning, and also that in the last resort the planners are ourselves.

Prophylaxis in Thromboembolism

THROMBOEMBOLISM is a systemic disease with focal manifestations. The ætiology of it is obscure; the diagnostic criteria are crude; and the clinical course, though usually benign, is always unpredictable and sometimes lethal. For several years surgeons, whose interest has been turning increasingly to groups of patients especially prone to thrombosis, have been asking for therapeutic guidance; and, despite vast blanks in factual knowledge which might have been expected to daunt the bravest, advice has been given in abundance. Unfortunately, some of it has been without experimental basis, some has been lacking in clinical sense, and the bulk has been woefully deficient in both. Our present degree of familiarity with thromboembolism resembles the doctor's understanding of anæmia before the days of red-blood-cell counts, hæmoglobin estimations, and hæmatocrit readings. We are incapable of recognising any but the grossest forms of the disease; and almost certainly we are lumping together pathological entities as different as chlorosis and vitamin-B_{12} deficiency.

What little theoretical understanding we do have is still based on the triad of causes enunciated with extraordinary vigour and lucidity by VIRCHOW,[1] though neither singly nor in combination do these provide a complete explanation. Experimentally we can precipitate thrombosis with ease and certainty by injury; but the clots tend to remain localised to the site of trauma and eventually disappear. Vascular stasis, the second factor in the triad, has become even more firmly entrenched in medical thought: yet this dogma derives in about equal parts from revelation, pious tradition, and a mass of uncontrolled clinical observation. WESSLER and DEYKIN [2] have confirmed that a stationary column of blood, included between two ligatures carefully applied to the dog's jugular vein, remains unclotted for many hours (much longer than it would in most of the specially coated glassware that we use in vitro [3 4]); and when the blood does clot, fibrin is deposited before prothrombin can be shown to have been consumed.[5] That under similar conditions firm and rapid clot formation is induced if homologous serum is injected into a distant part of the dog's circulation a few minutes before the ligatures are applied, lends weight to the third member of VIRCHOW's triad—altered coaguability. Unfortunately this finding does not explain what the alteration is.

WESSLER and DEYKIN emphasise that the thrombus formed in the isolated jugular-vein segment consists of a meshwork of fibrin in which cells are trapped: for many days it shows no lines of Zahn or other features that might distinguish it from a "postmortem" thrombus (despite the name, these are probably quite common during life). When such clots break off and lodge in the pulmonary circulation, even if many centimetres long they provoke only slight hæmodynamic changes; and soon they disappear. By contrast, much smaller thrombi which have matured for a few weeks in peripheral veins can initiate serious embolism with permanent lung damage and even death.

Any disease whose ætiology is so complex and so ill understood is fertile soil for exuberant therapeutic claims and counterclaims; and, if we remember the difficulties which surround bedside diagnosis and assessment,[6 7] initial scepticism towards yet another clinical trial seems not merely justified but even necessary. But such doubts will be disarmed by Dr. SEVITT and Dr. GALLAGHER, of Birmingham, whose paper we publish on p. 981. Their carefully designed and controlled trial of phenindione prophylaxis in injured elderly people promises to become a landmark in the management of this important group of patients, in whom we are only now beginning to recognise that even minor episodes of thromboembolism are commonly a starting-point of inexorably progressive cardiopulmonary disease.[8 9]

Judged by numbers of lives saved and amount of suffering prevented, pinning of the fractured femoral neck is the greatest technical advance in surgery of the past thirty years. What used to be the death-knell to thousands of otherwise fit elderly people today involves no more than two or three weeks in hospital,

1. Virchow, R. Gesammelte Abhandlungen zur wissenschaftlichen Medizin. Frankfurt, 1856.
2. Wessler, S., Deykin, D. *Circulation*, 1958, **18**, 1190.
3. Bizzozero, J. *Arch. path. Anat.* 1882, **90**, 261.
4. Allen, E. V., Barker, W. W., Hines, E. A., Jr. Peripheral Vascular Diseases. Philadelphia, 1955.
5. Wessler, S. *J. clin. Invest.* 1952, **31**, 1011.
6. *Lancet*, 1957, ii, 1101.
7. *ibid.* 1958, i, 465.
8. Ball, K. P., Goodwin, J. F., Harrison, C. V. *Circulation*, 1956, **14**, 766.
9. Zollinger, H. U., Hensler, L. *Schweiz. med. Wschr.* 1958, **88**, 1228.

provided that during this time they neither bleed nor clot to death. Unfortunately these twin dangers are still often represented as opposite and alternative extremes—a false notion hatched in test-tubes, taken up in text-books, and tamely accepted by clinicians. This notion accounts, in part at least, for the surgeon's reluctance to prescribe anticoagulant prophylaxis postoperatively. To exchange the risk of "spontaneous" thrombo-embolism for a slightly lesser risk of "drug-induced" hæmorrhage is an uninviting proposition; but not all seem to realise that a patient is more likely to bleed as a result of previous extensive clotting than as a result of reasonable anticoagulant therapy. Admittedly the mechanism which links trauma, thrombosis, and the tendency to sudden massive hæmorrhage is still obscure; but to attribute bleeding to anticoagulants merely because it strikes patients who, having had episodes of thromboembolism, are under treatment with these drugs is unsound and is bound to delay elucidation of the relation. The 70-year-old woman patient whose case is summarised by the Birmingham workers may have had post-thrombotic hæmorrhage; and one can hardly doubt that, had she not been rejected from the phenindione group because of peptic-ulcer symptoms, her death would have been ascribed to anti-coagulants.

Better founded is the widespread fear of an anti-coagulant "rebound" phenomenon. Attention to this risk is especially justified in postoperative cases where there is no indication for continuing therapy indefinitely. Conceivably it was partly responsible for the two cases of fatal hæmorrhage recounted by SEVITT and GALLAGHER, though other factors mentioned by them (including age) could well have accounted for both deaths. That the Birmingham trial does not give pat answers to all the questions it raises adds to rather than detracts from the validity of the main conclusions. The difference between the incidence of major embolism in the two groups—18% in the controls, and nil in patients on prophylactic phenindione—leaves little room for argument.

A decision to use routine anticoagulant prophylaxis raises the hard practical questions of who should control what, where, and how. In a busy traumatic surgical unit a good deal can be said for leaving supervision of dosage and response to the clinical pathologist. Despite his title, he is not always much of a clinician; but the risks of his missing the odd rhonchus (which is after all negligible compared to the risk of the patient suffering undetected myocardial infarction in the physical rehabilitation ward) is outweighed by his greater ability to keep a regular check on progress. Such a system cannot work unless two conditions are fulfilled. First a reasonable degree of mutual trust must prevail between the surgical and laboratory staff (a state which can be achieved by both sides concentrating on the patients' welfare rather than on each other's sensibilities), and secondly adequate space and staff must be provided for an anticoagulant unit. As a rule, from poky little corners of the hospital come poky little results—though the reverse, alas, is not necessarily true.

Prisons

IT is unfortunate that at this encouraging time of prison reform the authorities are burdened with more and more offenders. The report [1] of the Prison Commissioners tells of the greatest prison and borstal population ever—26,709 in April of this year. With 24,000 receptions, crimes of violence have prior place; "breaking and entering" comes second (7141), and it is the increase in these categories that accounts largely for the rise in the prison population. As expected, the rise is most obvious in the 16–21 age-group. Fluctuations in other classes of crime are small, but (with the exception of sexual offences) the trend is always upwards. As Baroness WOOTTON [2] has reminded us, such statistics are of little strict scientific worth although it is generally (and surely correctly) agreed that they represent a true rise in crime over the past three years. The numbers of women in prison (only about 4% of the total) now show the slow and retarded rise that they do when sex-incidence rates among adolescents are compared by ages. In mitigation it may be noted that the receptions under sentence, calculated per 100,000 population, have several times been higher during the past few years, so that some of the increase is evidently due to expanding population. Unhappily the reception of men not under sentence has increased by 5000 since 1957 to 44,000: this is a practice which, we suggested,[3] is too often used unnecessarily or unfairly. There was also a rise in receptions for non-payment of fine (half had not been given time to pay) although new powers to attach the earnings of defaulters at source will, it is hoped, reduce the numbers (over 6000) considerably. The proportion of men sentenced to under six months is still about two-thirds, and much doubt must remain whether such short sentences do not do more harm than good: many will agree with HOWARD JONES [4] that under existing circumstances offenders are more likely to be corrupted than cured.

In the matter of training, signs of continuing improvement are evident from the commissioners' report. "Inmate participation" is on the increase, prisoners' committees are springing up everywhere; of the two women's open prisons, for example, it is said: "... the women are being weaned from their reliance on the staff to organise their activities and make their decisions, and the very fact that many of them would prefer to be spoon-fed shows the need for a measure of independence." The Norwich system of open association has spread to 6 prisons and is about to start in 3 more; but the most notable advance along these lines is group counselling, lately introduced at Wakefield Prison and Pollington Borstal and described on p. 1022. Progress towards the real-life work situation is slow but perceptible: unfortunately the increase in contract work scarcely kept up with the greater numbers, and much of it, being breakdown and salvage work—stripping electric cables, for example—was of poor quality.

1. Report of the Commissioners of Prisons for the Year 1958. Cmnd. 825. H.M. Stationery Office.
2. Wootton, B. Social Science and Social Pathology. London, 1959.
3. *Lancet*, 1958, ii, 565.
4. Jones, H. Prison Reform Now. Fabian Research Series no. 203, 1959. See *Lancet*, 1959, i, 296.

Two more farms were bought and staffed, however, and four others are on the way. The use of normal employment from a pre-release hostel, pioneered in Bristol over five years ago, is now spreading widely and with apparent success, although no figures are given. As something just short of release on licence, this measure deserves well and could greatly ease overcrowding, given the right cooperation from labour authorities and employers. The need for such a graduated re-entry into society is increased by the inability of the present prison aftercare services to give more than a small part of the necessary help. Pioneer ventures, such as Norman House, are rare, and the attitude of bitter cynicism in many prisoners is easy to understand.

With an increase in committals of about 700 to 3047 the borstals faced an exacting task, and despite the opening of 4 new institutions most youths still wait for two months in local prisons before reaching reception centres. The report comments:

> "... the type of boy committed is certainly no better than in the previous year, and there appeared to be even more boys whose homes showed a background of divorce, separation, maladjustment and unhappiness. One governor felt strongly that violence to the person and property was but a reflection of violence to children in their upbringing. Thus a greater number appear to have more difficult personal social problems than hitherto; boys difficult because unloved, unloved because difficult. Borstal cares for all who come but is not necessarily the best medium of training for some of the boys."

Of 113 girls discharged in 1958, only 11% had not been deprived of one or both parents' care during childhood. The sentence to borstal being an indeterminate one of up to three years, most boys seemed at first not to think constructively about discharge and to waste much of their training; so aftercare work is now started "literally after sentence and continued throughout the boy's training". Similarly during inpatient treatment of neurotics it has been found necessary to plan for discharge from the earliest days.[5]

On the health side, it is good that outside hospitals are being used more than before, a logical development which may reduce recidivation among borstal boys at least.[6] The incidence of insanity and mental defect in prisoners in 1958 was lower despite the greater numbers —which probably reflects greater recourse by the courts to specialist reports and civilian psychiatric facilities. Discipline has remained satisfactory although escapes are causing the commissioners much concern. They record that corporal punishment was ordered only 3 times, despite 142 acts of violence against officers. These punishments were not confirmed by the Secretary of State and were not, therefore, given (in 1957 the birch or cat was used on 6 occasions). Though obviously in no position to assess their "cure" rate for all offenders, the commissioners state that, over five years, about 85% of star-class men do not return to prison.

At a net cost to the Exchequer of only £11,300,000, the prison service is a small item in our annual budget and would be cheap at half as much again.[7] We hope the Government will be more generous in future, so that progress can be accelerated. As it is, in their own way, and against an immense backlog of hostility between prisoners and staff and entrenched prejudice, some prisons are approaching the "therapeutic community" quite rapidly, as the surprising report about group-counselling at Wakefield demonstrates. Moreover, day prisons analogous to day hospitals already exist for young offenders as "attendance centres", and the principle could easily be extended to short-sentence adults. The graded use of occupation, incentives, responsibility, and half-way (pre-release) hostels are all measures of reablement common to both prison and mental-hospital systems. The future may well disclose a closer and closer identity between these two streams of therapeutic endeavour.

5. *Lancet*, 1959, ii, 221.
6. Ogden, D. A. *Brit. med. J.* 1959, i, 432.
7. *Times*, Aug. 21, 1959.

Annotations

DENTISTS AND ANCILLARIES

In his letter on p. 1030, the General Secretary of the General Dental Practitioners Association, Mr. Ransome Markham, implies that the failure to fill the gaps in the dental profession can be put down mainly to conditions of general practice under the National Health Service. Undoubtedly there is much dissatisfaction among dental practitioners; but we question whether, to a young man or woman weighing the attractiveness of prospective careers, this dissatisfaction is commonly crucial in deciding against a career in dentistry. After all, one effect of the National Health Service has been virtually to guarantee to all newcomers to the profession, immediately on qualification, a choice of well-paid assistantships in general dental practice in almost any part of the British Isles—often with a house or flat, and sometimes even with the use of a car, as added inducement. This state of affairs, having existed for some time, must be known to aspirants who have made even preliminary inquiries about dentistry as a career. If they are still not drawn to the profession, we may conclude that, for many at least, the apparently unattractive nature of the work of a dentist is unlikely to be outweighed by the advantages of income, status, or security which it could offer. When the scientifically minded or manually dexterous student has the choice of openings which an expanding economy offers the ambitious rising generation today, it is less probable than formerly that he will choose dentistry, which, unless he is specially interested, may well appear relatively restricted, unadventurous, and without glamour. The community will be well advised to expect continuing prosperity to lead to the dental profession being so reduced in numbers as to be unable to fulfil its role unaided.

The situation could be transformed, however, if there were enough ancillaries to relieve dentists of the simpler operations of dentistry. Trained only to perform certain specified straightforward operations, and working under the direct personal supervision of a dentist, these ancillaries should neither threaten the position of the dental profession nor lower the standards of treatment of the public.

The Dentists Act does no more than authorise an experiment in the training and employment of dental ancillaries; and, in view of the critical state of affairs referred to by Mr. Ransome Markham in his letter, it is

a great pity that there has been so long a delay in carrying out this provision of the Act. The first student dental ancillary will not begin her training before next October, and M.P.s do well to ask the Minister whether such delay can be justified. Such questions could usefully have been asked in Parliament much earlier.

DOGS' DELIGHT

EXCEPT when crossing on a stormy day we must be grateful to the English Channel. It has protected us from Boney, Hitler, and rabies—and those who have lived in countries where rabies is endemic know that our gratitude is well justified. Not that all our dogs are innocent of causing human disease. Perhaps half of them have leptospiral infections, and it is hard to explain why human infection is so rare. They harbour salmonellæ. They suffer from tuberculosis, but whether they catch it from their owners or vice versa no-one can yet be sure. Especially when young they are a source of ringworm. They barge into young children, who fall and crack their skulls. They upset old ladies, who fracture their femurs. They run into the road and cause fearful accidents (which probably would not happen if motor-drivers went more cautiously). And they bite. Surgically dog-bites are not without interest. Like all animal bites they tend to heal slowly. They are often infected with out-of-the-run bacteria, such as *Pasteurella septica* and *Hæmophilus bronchisepticus*, derived from the animal's mouth, and they have caused tetanus. But since we have no rabies dog-bites are not taken very seriously.

Because of a large reservoir of wild canines (to say nothing of bats) it has been impossible so far to abolish rabies in North America, and for this reason every dog-bite has a significance which is absent here. At the same time the inhabitants are renowned for their kindness and humanity and enjoy keeping pets as much as anyone. If anyone could provide rational answers to the questions about which dog is likely to bite whom—and when—some anxieties might be dispelled. A recent report examines this virgin field of inquiry in every aspect, from data collected in Pittsburgh, Pa.[1]

More men than women are bitten, but more bitches than dogs do the biting. As with us, postmen, brush salesmen, and veterinary surgeons are favourite victims. 76% of those bitten are under 20. Wounds on the arms and legs are about equally common and those of the face the most serious. About a third of the bites occurred when the victim was playing with the dog, and the same number "were attributed to human activities which caused the dogs to bite". (Having watched some small children playing with dogs we think the line between these groups must be thin.) The rest are attributed to sheer unadulterated malice. Young dogs are likelier to bite than their elders: they have "poor adjustment towards people". Comparison of the biting propensities of various breeds is difficult because the classification of the American Kennel Club reads strangely to us. "Working dogs" (boxers, collies, and Alsatians) are the most savage; but it is worth remembering that few of these "work" in Pittsburgh. Sporting dogs (i.e., gun dogs) come next, and terriers after them. "Hounds", on the other hand, are relatively harmless; but what hounds are kept in the Sheffield of the U.S.A. is a puzzle. The largest class is labelled "mixed"; and we suspect that these are what we, more rudely, term mongrel; but there is another class—"unrecognised". These canine plebs are numerous, but no more than average biters. Dogs given to fighting are said to seldom bite anyone but the booby who tries to stop their fun. Some dogs are always biting people.

In general all this information fits in with our experience. Whether it will influence anyone in the choice of a pet is another matter. There is no mention of police action in this study. One dog is reported to have bitten eight people, and in this country the owner of such a pest would have been before the magistrates a long time ago. We love our pets—but they have got to live by our rules and not their own.

1. Parrish, H. M., Clack, F. B., Brobst, D., Mock, J. F. *Publ. Hlth Rep., Wash.* 1959, **74**, 891.

REST AND RHEUMATOID ARTHRITIS

John Hilton [1] urged the desirability of rest in joint disease, pointing out that immobility did not damage healthy joints. The value of rest in the management of rheumatoid arthritis is a matter of opinion, and, while most physicians believe that it is beneficial in acute phases, there is no agreed foundation for such statements as "Bed rest is *absolutely* necessary for every patient." [2]

Mason and Wenley [3] admitted 40 patients with severe rheumatoid arthritis to beds previously used for the treatment of tuberculosis at Black Notley Sanatorium. The patients, who had had the disease for an average of 9·4 years, were managed on standard sanatorium lines, with long-continued rest in bed and splinting. Analgesics and iron were the only drugs given, while physiotherapy and other rehabilitation procedures were limited to the last few weeks of hospital stay, which averaged six and a half months. By the time of discharge there was a slight decrease in disease activity in the group of patients; the mean erythrocyte-sedimentation rate had decreased from 50 to 38 mm. in the first hour (Westergren) and the mean hæmoglobin had risen from 69 to 79%. The most significant change was in functional capacity, expressed as grades I (fit for all normal activities), II (some restriction but complete independence), III (some dependence), and IV (complete dependence). Initially all 40 patients were equally distributed between grades III and IV. By the time of discharge 3 of the 20 in grade III had gone up to grade II, 14 remained in grade III, and 1 had deteriorated to grade IV (the 2 other patients having discharged themselves after one and two months' stay). Of the 20 in grade IV, 7 remained there and 13 had moved up to grade III. Further improvement was evident at later follow-up.

This degree of improvement must be assessed against what is known of the natural history of rheumatoid arthritis. A randomly selected control series could not be collected in the Black Notley experiment for the interesting reason that the number of patients who would accept admission to a country hospital fifty miles from their homes for many months was barely sufficient to fill the available 10 beds, let alone to provide an equal number of controls. Accordingly, Mason and Wenley turned to the important study in Edinburgh by Duthie et al.,[4] who conducted a six-year follow-up in cases of rheumatoid arthritis from the time of their admission to hospital (necessitated by the severity of their disease). The average duration of the initial hospital stay was nine to ten weeks. Of the 307 patients in the original group, the distribution in grades I, II, and IV on admission

1. Hilton, J. On the Influence of Mechanical Rest in the Treatment of Accidents and Surgical Diseases, and the Diagnostic Value of Pain. London, 1863.
2. Talbot, J. H., Lockie, L. M. Progress in Arthritis; p. 115. New York, 1958.
3. Mason, R. M., Wenley, W. G. *Ann. rheum. Dis.* 1959, **18**, 91.
4. Duthie, J. J. R., Brown, P. E., Knox, J. D. E., Thompson, M. *ibid.* 1957, **16**, 411. See *Lancet*, 1958, i, 894.

to hospital was 0%, 35·4%, 42·6%, and 22·0% respectively. On discharge from hospital the corresponding figures were 11·3%, 64·2%, 24·1%, and 0·4%. At the time of the last examination six years later the figures for the available 247 patients were 23·5%, 40·5%, 26·7%, and 9·3%, indicating a relatively benign prognosis in what is generally regarded as a progressive and crippling disease. The Edinburgh workers did not consider that the conservative regimen of treatment used in their study was likely to have had any specific effect on the course of the disease, though "the value of general and local rest in reducing the activity of the disease process at least temporarily should not be entirely discounted".

The Black Notley experience of sanatorium treatment in severely disabling rheumatoid arthritis, though of interest, gives little indication of the actual value of rest in the disease. This can be decided only by a controlled trial covering cases in all grades of severity.

ABDOMINAL ANEURYSMS

FEW of us would put a new engine into a car whose body was unlikely to see the year out; and likewise we should perhaps sometimes hesitate before undertaking grafting operations in cases of abdominal aneurysm. Sommerville et al.[1] report that, in the 20,201 necropsies at the Mayo Clinic in 1925–54, the prevalence of abdominal aneurysms was 0·8%; the mean age was 75·5 years, but women with this disorder were on average 8 years old than men. Of the 172 cases reviewed by Sommerville et al. 32 had symptoms or signs which had led to diagnosis before death. The important features are well recognised: abdominal pain, particularly to the left and below the umbilicus; back pain; acute abdominal pain due to rupture; inguinal or testicular pain; acute leg ischæmia or claudication due to thrombosis; and a palpable expansile mass. Antemortem diagnosis depends very largely on the size of the aneurysm: of the 55 cases of aneurysms more than 4·5 cm. in diameter, 55% had been recognised before death: of the 117 cases of smaller aneurysms the diagnosis in life had been reached in only 2. When the aneurysm is larger than 4·5 cm. its size did not seriously influence the clinical features or progress. Contrary to the usual belief, fusiform aneurysms tended to cause more symptoms and more complications than saccular aneurysms of like size.

A good deal is now known about the prognosis in clinically detectable cases. Estes [2] found, not surprisingly, that the mortality-rate in patients with abdominal aortic aneurysms was consistently higher than that in a comparable group without aneurysms. Of his series of 102 patients, 67% survived for a year from the time of diagnosis, 58% for two years, and 49% for three years. In a normal group of similar age and sex distribution, about 85% are alive at three years; which underlines the poor prognosis in the arteriopathic patients. Many died of aneurysmal rupture, but more died of coronary or cerebral thrombosis.

The dramatic advances of vascular surgery and parasurgical techniques in the past decade have encouraged a tendency to believe that abdominal aneurysm should invariably be resected and replaced by a graft. The argument runs smoothly: the serious prognosis associated with abdominal aneurysms; the low surgical mortality-rate; and the advantages in tensile strength of the prosthetic materials, particularly 'Dacron' and 'Teflon', over homografts. It is with this in mind that Sheranian et al.[3] have reviewed 135 cases submitted to operation (how many aneurysm cases were diagnosed but rejected for surgical treatment is not stated). At operation only 110 of the 135 aneurysms were resectable; and of the 110 patients, 18 died in hospital. There were thus left 92 patients with resected aneurysms and inserted grafts, of whom 81 were followed up for three years, at the end of which 85% were still alive. This they compared with the expected survival-rate of 89·9% in a "normal" control group. But is this comparison justified? First, how many patients were excluded before operation? Secondly, if it is assumed that 85% of the 11 patients who survived resection but could not be followed up were alive, and that in the 25 advanced cases where resection proved impossible at laparotomy the patients were dead, then the overall three-year-survival rate was about 58%.

Abdominal aneurysms have possibly been regarded in the past few years as an initiation test to surgical manhood, and the time has come for reappraisal. Certainly it is hard to substantiate the common belief that any abdominal aneurysm which can be diagnosed should be resected. Without operation most patients die with abdominal aneurysm rather than because of it. Surgery is manifestly justified if the aneurysm is causing pain, if it is increasing in size, or if thrombosis develops. Such selection would worsen the surgical mortality figures, but would, we believe, be to the benefit of the patients.

PSYCHOPHARMACOLOGIA

THAT drugs used as medicines should have a psychological effect is so obvious that the issue of a new journal called *Psychopharmacologia* [4] may surprise many. In fact, only quite recently have pharmacologists turned their attention to psychic and "behavioural" influences of drugs. The sedatives, hypnotics, and analgesics on which pharmacology concentrated since early in the 19th century were recognised as having a psychological effect only in that they reduced or abolished consciousness and awareness; and sleep, narcosis, and suppression of pain were interpreted from the neurophysiological angle. Little interest was shown in the side-effects or after-effects of these or other drugs on the patient's feeling and experience. This omission is now being repaired; and the new journal is a welcome aid.

The first issue promises well. No effort is made to conceal the difficulties of method in this specialty, where neurophysiology overlaps with or touches on the so-called behavioural sciences including psychology. The surveys on behavioural pharmacology and on the use of lithium in psychiatric treatment will, we hope, be followed by further critical reports on similar questions. Comparative studies on cross-tolerance of lysergic-acid derivatives, and on convulsive treatment with drugs, set the pattern for future investigations of a similar kind. Original studies of special problems will always be the principal content of such a journal, and will command attention so long as the technicalities do not become so complex that pharmacologists, neurochemists, neurophysiologists, neurologists, and psychiatrists—the scientists invited to constitute an integrating discipline—cannot understand one another.

Dr. ARCHIBALD GILPIN, physician to King's College Hospital, London, died on Nov. 29 at the age of 53.

1. Sommerville, R. L., Allen, E. V., Edwards, J. E. *Medicine, Baltimore*, 1959, **38**, 207.
2. Estes, J. E. *Circulation*, 1950, **2**, 258.
3. Sheranian, L. O., Edwards, J. E., Kirklin, J. W. *Surg. Gynec. Obstet.* 1959, **109**, 309.
4. *Psychopharmacologia*; vol. 1, no. 1; August, 1959; D.M. 9.60. Annual subscription: 1959, D.M. 40; 1960, D.M. 80. Published by Springer-Verlag, Berlin-Wilmersdorf, Heidelberger Platz 3.

Public Health

OUTBREAK OF PARALYSIS IN MOROCCO DUE TO *ORTHO*-CRESYL PHOSPHATE POISONING

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WE went to Morocco on Sept. 25, 1959, as " temporary advisers to the World Health Organisation in order to advise the Moroccan health authorities in investigating an outbreak of a paralysing disease of unknown origin ". A full account of the outbreak is in preparation in association with colleagues in Morocco, but in view of recent newspaper reports a short account of our personal experience may be of interest. Moreover, cresyl phosphates, which commonly include *ortho*-cresyl phosphate (O.C.P.), have many industrial uses, because they are very heat-stable and are also important plasticisers. Although O.C.P. is notorious among industrial users for its toxicity, and it is used only with strict precautions, the possibility of poisoning must not be forgotten.

When we reached Morocco, a large amount of epidemiological and statistical information had already been collected by the Moroccan health authorities, and was made avilable to us in Rabat, the administrative capital of Morocco, where we had our headquarters.

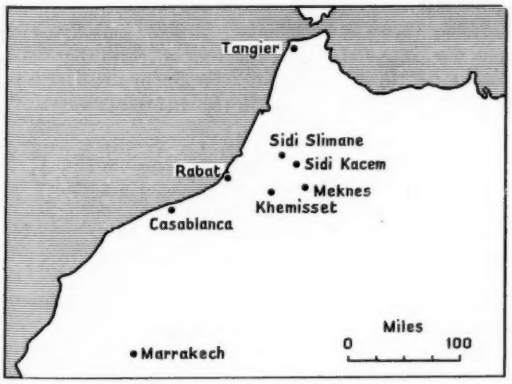
EPIDEMIOLOGY

To summarise the information we were given:

1. The first cases occurred between Aug. 31 and Sept. 2. The incidence then rose until between Sept. 18 and 24 200–300 new cases were being reported daily. By Oct. 2, when we left Morocco, more than 2000 cases were already known and it was clear that more were to be expected.

2. The outbreak was centred on Meknes and the towns in the vicinity, notably Sidi Slimane, Sidi Kacem, and Khemisset. Of the few patients seen elsewhere, almost all had recently been in Meknes. One man developed the disease in Marrakesh fourteen days after leaving Meknes.

3. Within Meknes itself the distribution of cases varied sharply from district to district. With one exception (a man who had adopted the Moslem way of life), no cases were seen among the Europeans, among the Jews, or among the better-to-do Moslems. The cases were grouped in distinct areas on the periphery of the town where the poorest of the Moslem population live. Even in these areas, however, the distribution was uneven in that the poorest of the poor were largely spared.



4. Both sexes and all ages were liable to the disease, but the chief incidence was in adult women, adult men, and older children—in that order. When there was more than one case in the same family they tended to follow one another at intervals of four to five days.

5. From Sept. 14 to 18 over a quarter of a million people visited Meknes and its neighbourhood to celebrate the feast of the birth of the Prophet. So far as was known, not one of the visitors had developed the disease either in Meknes or after leaving it. It is usual for such visitors to bring their own food with them.

6. A company of 100 soldiers was stationed at Meknes during the outbreak. Only 2 of these developed the disease, and both were unusual in being accustomed to eat in the town, not in barracks. Similarly no cases were seen in the prison in Meknes, but a few prisoners developed the disease within a few days of their release.

CLINICAL PICTURE

In the typical case, the illness began with aching pain and tenderness in the calf, followed by paræsthesiæ and loss of superficial sensation of stocking-and-glove distribution. After a day or two the disturbance of sensation decreased and might disappear, and at about the same time motor weakness appeared, involving first the muscles of dorsiflexion and eversion of the foot and a little later the calf muscles. Later still the muscles of the hand were commonly affected also. Only the more severe cases were admitted to hospital, and victims of the disease who were not in hospital could easily be identified at a distance by their ungainly high-stepping gait.

On examination all voluntary movements below the knee were found to be lost, and although in exceptionally severe cases the muscles of the thigh and even of the pelvic girdle might be affected, it was often surprising how abruptly the weakness stopped at the level of the knee-joint. The hands might be spared, but more commonly there was obvious weakness of the intrinsic muscles of the hand, which developed a few days after the weakness in the lower limbs. Muscular wasting was not conspicuous, but no patient had been paralysed for more than three weeks by the time we saw them. The tendon reflexes in the upper limbs were commonly preserved; and although, as might be expected, ankle-jerks were usually diminished or absent, it was sometimes surprising that even in cases with severe weakness the ankle-jerks were nevertheless obtainable. The knee-jerks were usually exaggerated, in contrast to the predominantly lower-motor-neurone type of weakness distally. The superficial reflexes were normal, with the exception of the plantar reflexes which were necessarily absent when movement of the toes was paralysed.

Signs of general ill health were uncommon. About one-third of the patients, however, had a history of recent diarrhœa. Some patients had had a little transient fever and some a shortlived bradycardia, noticed within a few days of their admission to hospital. All routine investigations were negative, including analysis of the cerebrospinal fluid and of the blood.

The picture, therefore, was essentially one of acute peripheral neuritis in which the distribution of the weakness was overwhelmingly distal. In addition there were less striking signs of an upper-motor-neurone lesion.

ÆTIOLOGY

Opinion was divided whether the disease was due to an infection or to poisoning.

Infection.—There was a strong *a-priori* case to suggest infection, probably by a virus. In favour of this was the appearance of a few cases followed in two to three weeks by an explosive outbreak; the fact that it attacked the poor, whose mode of life favours dissemination of infection by fæces, nasopharyngeal secretions, or insect vectors; and its occurrence in one subject as much as fourteen days after he left Meknes. If, however, this

was an infection, it must be one not hitherto described, and moreover it must carry a high clinical attack rate among the susceptible population. These considerations made it difficult to account for the distribution described.

Poisoning.—In favour of the toxic theory was the fact that a number of poisons can produce peripheral neuritis. Against it was the disseminated distribution and the evolution of the epidemic over weeks. Moreover, so far as was known, no essential change had taken place recently in the way of life of the people of Meknes, nor did this differ essentially from that of the inhabitants of other towns.

FINDINGS

A visit to Meknes convinced us that the infective theory was untenable.

In Borj Moulay Omar, a suburb of Meknes where the standard of living is low, both the poor and very poorest sections of the population were so closely intermingled that it was impossible to conceive of an infection attacking one section and sparing the other. It was equally impossible to imagine that one section could react to an infection as "a virgin population" while the other section reacted as an immune community. Finally, those conditions favouring the spread of infection enumerated above bore more heavily on the poorest of the poor, among whom the incidence was lower. This opinion was confirmed by the lack of infection among the visitors to Meknes for the festival. These visitors had returned to their homes in all parts of the country, and had they been exposed to a highly infectious illness they must have contracted the disease or acted as carriers. Whether the incubation period was four to five days (the shortest possible) or fourteen days (the longest), new cases must have appeared by then in different parts of the country. No such cases had been seen.

By contrast the toxic theory received overwhelming support.

The doctor in charge of the dispensaries at Meknes told us that he had recently seen samples of cooking oil which were as dark as old motor oil and that some patients believed that this oil was responsible for the illness. One family had been so suspicious that they gave some food cooked in this oil to their dog. As the dog showed no immediate sign of illness they ate the food themselves. Within a few days both the family and the dog were affected.

After leaving Borj Moulay Omar we visited a certain quarter of the medina—the old Arab town, occupied largely by Arabs of the artisan class—where there had been a severe but sharply circumscribed outbreak. In a grocer's shop in this area we found and bought a coloured bottle three-quarters full of very dark oil, bearing a trade name of a cheap brand of olive oil. Other bottles, of colourless glass, bearing the same trade name were seen in the same and neighbouring shops containing oil of the normal yellow colour. In the meantime, the health authorities had investigated the manufacture and distribution of cooking oils in Meknes and discovered that the same wholesaler supplied oil to all affected areas. Finally those questioned declared that the dark oil had been offered for sale only during the past month.

There was thus strong evidence that at least one consignment of cooking oil had been contaminated and was the cause of the outbreak. The contaminant was, we then supposed, a mineral oil. In the first place the clinical picture corresponded closely to that described in outbreaks of O.C.P. poisoning seen in Germany and Switzerland since 1939 and in the U.S.A. before the war, and O.C.P. is added to certain oils for special purposes. Secondly, this hypothesis accounted for the pattern of the outbreak: the well-to-do people could afford to buy better brands of oil, while the very poor could hardly afford to buy any oil at all. It explained the absolute immunity of the Jews, who have their own market. It also accounted for the extraordinary immunity of visitors to Meknes for the festival, since such visitors ordinarily bring their own food. Finally, the period during which the dark oil had been on sale corresponded precisely to the period of the outbreak.

The oil bought at the grocer's shop in the medina of Meknes, and other samples of "olive" oil bought both in affected and unaffected areas, were analysed. Before we left, the Institute of Hygiene at Rabat had demonstrated the presence of phosphates and cresols. In this country a well-known industrial company with a highly specialised knowledge of oils very kindly undertook further examination of the samples. This firm demonstrated that the "olive" oil obtained in the medina at Meknes contained about 33% of vegetable oil and, much to our surprise, no mineral oil. The firm then showed that the toxic oil was a man-made lubricating oil containing nearly 3% of mixed cresyl phosphates, mainly the *meta*—and *para*—compounds. These oils are synthesised in order to withstand the very high temperatures to which oils used to lubricate turbo-jet engines are exposed. They are very expensive, but as engine design alters and the science of lubrication progresses the oils periodically become out of date, and are then of little value. The firm was able to identify the specification to which the oil was made, and it was one that is no longer current. Cresyl phosphates occur as a mixture of *ortho*-, *meta*-, and *para*- compounds; but, as the dangers of the *ortho*- compounds are well known in the industry, manufacturers remove as much of them as possible.

DISCUSSION

Ortho-cresyl phosphates are highly toxic to the nervous system. Tri-ortho-cresyl phosphate, though by no means the most toxic member of the group, is nevertheless the best-known, and was held responsible for the great outbreak of paralysis in the U.S.A. in the early 1930s. The disease then earned the name of Jake paralysis because the O.C.P. was present in a soft drink called "Ginger Jake" or "Jamaica Ginger".

The clinical picture is well documented (Burley 1932, Jordi 1952, Hunter 1955), but less is known of the pathology, at any rate in man, because even in severe poisoning the mortality is remarkably low. In the Moroccan outbreak the clinical picture was characteristic, and we agree with Burley that it must be virtually pathognomonic. At the time of our visit no-one had died of the disease, nor has any death been reported since.

The prognosis depends on the severity of the paralysis. Those with distal weakness alone recover well, but commonly take at least a year to do so. Those with weakness of proximal muscles in addition recover less completely, and those with marked signs of damage to the spinal cord are usually left permanently disabled. In the Swiss outbreak (Jordi 1952) very severe poisoning followed ingestion of a single large dose, and 25% of the patients were left permanently disabled. In the Moroccan outbreak, however, traces of O.C.P. were consumed over many days, and fortunately the great majority of cases that we saw were mild. In all probability therefore in a year's time the great majority will be well on the way to recovery.

SUMMARY

A personal account is given of a visit to Morocco to assist in investigating an outbreak of paralysis. 2000 cases had occurred before we left Morocco and the outbreak continues. It proved to be due to poisoning by *ortho*-cresyl phosphate, present in lubricating oil sold as "olive oil". The lubricating oil was man-made and was synthesised to withstand the very high temperatures pertaining in turbo-jet aircraft engines.

We wish to thank our medical colleagues in the administrative and clinical services in Morocco for their unreserved cooperation during

our visit. The industrial firm in this country which conducted the analysis wishes to remain anonymous, but we are grateful to its research staff for their invaluable work.

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The Moroccan Situation

In Geneva on Nov. 18 Dr. Ranhima, secretary-general of the Moroccan health ministry, met representatives of the World Health Organisation's regional office for Europe, and other bodies, to discuss further practical aid for the Moroccan Government in dealing with their cases of *ortho*-cresyl phosphate poisoning. At the request of the office, visits to Morocco have been paid by Dr. Smith and Dr. Spalding, and by Professor Leroy (Rennes, France), who was asked to recommend measures for the treatment and reablement of the victims—now estimated at about 10,000.

Difficulties are the greater because Morocco, with a population of some 10 million, has only 17,000 hospital beds; and the child victims are being given priority.

The proposals now made are that a special hospital should be established at Meknès, to work in liaison with 17 treatment centres in different parts of the affected region. Each centre should aim at treating 400 victims, and will require a staff of physiotherapists and health assistants. They can be housed in tents or temporary buildings, with mobile kitchens; but each will need "a large quantity of equipment such as crutches, water-baths, sunbaths, halters, special skates, and other rehabilitation apparatus".

Health in Non-ferrous Foundries

The second report of the Joint Standing Committee on Safety, Health, and Welfare Conditions in Non-Ferrous Foundries [1] is devoted to the known and potential health risks in this branch of the foundry industry.

Dr. W. D. Buchanan reviews concisely the information available on such subjects as pneumoconiosis, metal fume fever, and lead absorption and poisoning. He also deals briefly with the risks inherent in the use of beryllium, cadmium, manganese, phosphorus, selenium, tellurium, and vanadium. Such a list shows the diversity of toxic metals used in the various divisions of the non-ferrous founding industry—a diversity greater than that encountered in iron and steel foundries. In addition there are the risks common to all types of foundries, as for example the fumes from core oils and binders, other mineral oils, drying stoves, mould drying, and furnaces. Sulphur dioxide contaminates the air of magnesium foundries and is likely to cause chronic bronchitis; bichromate solutions are used to etch magnesium castings and carry with them the risk of dermatitis and ulceration of the nasal septum.

The fluxes and degassing agents used in different types of non-ferrous foundries all carry with them toxic risks. Examples are chlorine, hexachlorethane, fluorides, manganese, and sulphur. In two comparatively new moulding methods—the carbon dioxide process and shell moulding—the health risks can be estimated from the substances used; but more study of them is necessary. In fact, Dr. Buchanan shows clearly the need for an extensive survey of the health risks throughout each division of the non-ferrous foundry industry. The committee recommends that such a survey should take place, and further states that medical supervision of the workers is desirable, wherever it can be arranged.

1. H.M. Stationery Office. 1959. Pp. 24. 1*s*. 9*d*.

Sterilisation of Syringes

This week the health committee of London County Council submitted to the Council a proposal to use, as an experiment, in health division 2 (Hampstead, Paddington, St. Marylebone, St. Pancras, and Westminster) the central syringe service at Paddington Hospital. 8*d*. will be payable for each syringe sterilised. In the rest of the county, for each injection a fresh syringe and needle are to be provided, instead of a freshly sterilised needle only as at present.

Preservatives in Food

The Food Standards Committee has submitted proposals [1] for amending the Public Health (Preservatives, &c. in Food) Regulations.

If the committee's recommendations were accepted all the foods at present permitted to contain preservative would continue to be allowed to do so; but modifications are suggested in the provisions applying to fruit pulp and other fruit products, soft drinks, pickles, and sauces. Changes are also suggested in the present provisions for cured meats. The more important suggested additions to the list of foods permitted to contain preservatives are for bread to contain propionic acid; for flour confectionery, cheese, and certain food adjuncts to contain sorbic acid; and for various canned foods and cheese to contain the antibiotic, nisin. The provisions relating to the treatment of citrus fruits have already been amended in accordance with the committee's recommendations.

In formulating its recommendations the committee has been guided by the principles that preservatives should be employed only if their use has been expressly authorised; that additions should be permitted only in those foods where they have been shown to be necessary or advantageous, and then only in the amounts needed to achieve the desired effect; and that the addition should not give rise to any health hazard.

Representations on the committee's recommendations should be submitted by March 25 to the Assistant Secretary, Food Standards Division, Ministry of Agriculture, Fisheries, and Foods, Great Westminster House, Horseferry Road, London, S.W.1.

Conference

LIVER DISEASE

A MEETING of the American Society for Study of the Liver was held in Chicago on Nov. 5, with Dr. R. B. CAPPS presiding.

J. W. GRISHAM (St. Louis) had made studies with the electron microscope on the liver of ethionine-treated rats; he had noticed disorganisation of the cytoplasm, and the mitochondria showed great enlargement (megamitochondria). CARROLL LEEVY and coworkers (Boston) had used tritium-labelled thymidine as an index of deoxynucleic-acid synthesis and hence of regeneration. After hepatic insult by carbon tetrachloride D.N.A. synthesis was noted throughout the hepatic lobule. The stimulus for regeneration therefore did not only affect the centrizonal areas where necrosis was maximal. They could not demonstrate a humoral factor which controlled hepatic regeneration.

H. CULP and coworkers had achieved homœotransplantation of the dog liver. The longest survival had been $6\frac{1}{2}$ days. Deaths were due to technical difficulties and to the homœotransplant reaction. WADE VOLWILER and his group (Seattle) could maintain an isolated perfused calf liver for up to 26 hours. The organ remained sterile for 26 hours. The preparation produced bile and cleared bromsulphalein from the blood. Hepatic lymph could also be collected. This procedure could clearly be a valuable experimental tool.

1. Food Standards Committee: Report on Preservatives in Food. H.M. Stationery Office. Pp. 70. 4*s*. 6*d*.

RUTH C. HARRIS (New York) described three infants with congenital heart-disease, usually Fallot's tetralogy, who exhibited an obstructive form of jaundice. Obstruction to major bile-ducts could not be shown and the mechanism of the jaundice was unknown. An equally obscure type of cholestatic jaundice was described by M. H. STAUFFER and colleagues (Mayo Clinic) in association with longstanding ulcerative colitis. H. POPPER (New York) wondered whether this might be genuine " chronic cholangitis lenta " due to ascending bacterial infection from the colon.

I. M. ARIAS (New York) described five mothers who bore infants with deep jaundice and kernicterus. The infants were not premature and blood-group incompatibility was excluded. Lathe and Walker have described activity in the serum of pregnant women which inhibits the conjugation of bilirubin by liver slices. The sera of the two mothers tested by Arias showed about twice the inhibitory activity of normal pregnant women.

A symposium on toxic hepatic injury was under the chairmanship of H. POPPER (New York). Jaundice due to drug therapy was classified by V. A. DRILL (Chicago) into that due to direct toxic action (e.g., chloroform), that due to hypersensitivity (e.g., chlorpromazine), and that due to constant interference with the metabolism of bilirubin (e.g., methyl testosterone or norethandrolone). G. KLATSKIN (Yale) emphasised that those causing direct toxic action did so constantly if the dose was large enough; experimental animals were affected and the same lesion developed in all individuals and species after a short incubation period. In contrast, drugs in the hypersensitive group caused jaundice in only a small number of individuals in a manner unrelated to dose and duration; no lesions were caused in experimental animals and the latent period and the lesions seen were variable from drug to drug and patient to patient. Jaundice was often preceded by a " hypersensitive " reaction with fever, rash, arthralgia, albuminuria, and eosinophilia. There are major differences from the usual " hypersensitivity " syndrome, for circulating antibodies to the drug cannot be demonstrated and skin sensitivity is unusual.

B. BRODIE (Bethesda) remarked that most drugs are made less fat-soluble by enzymes in the liver so that they can be excreted by the kidneys. These enzymes are present in hepatic microsomes. There were great species and even sex and strain differences in the metabolism of drugs. P. N. MAGEE (Carshalton) had studied the toxic effects of dimethyl nitrosamine on the liver and noted an interference with hepatic cellular microsomes. J. Y. JUDAH (Wistar Institute) reported a rise in serum enzymes after thioacetamide even before signs of hepatic damage could be seen histologically, and H. SHAY (Philadelphia) had noted increases in serum transaminases in patients receiving chlorpromazine before they became jaundiced.

S. HARTROFT (St. Louis), commenting on the similarity of the lesions induced in the liver by iproniazid and by virus hepatitis, wondered whether iproniazid might induce activation of the virus causing infective hepatitis. H. POPPER (New York) thought this unlikely because the hæmagglutination test of Havens was usually negative, and in one case of iproniazid hepatitis " virus " particles could not be seen in the liver by electron microscopy. This latter technique had also been used by F. SCHAFFNER (New York), who had found changes in the bile canaliculi in the liver of patients with norethandrolone (' Nilevar ') toxicity. S. SHERLOCK (London) reported three patients in whom chlorpromazine jaundice had lasted more than six months. The picture might be confused with primary biliary cirrhosis but the onset was more acute and ultimate recovery seemed to ensue.

Special Articles

GROUP COUNSELLING IN WAKEFIELD PRISON

FROM A PSYCHIATRIC CORRESPONDENT

EIGHTEEN months ago a psychotherapist with long years in forensic psychiatry said to me that although he had made a promising start with group discussions of prison matters among prison officers, the bitterness between them and the prisoners would prevent mixed group methods being used for a very long time. The encouraging start made in Wakefield Prison (parallel with similar developments in the United States) with group discussions between prison officers and prisoners has therefore impressed many people very forcibly.

THE PRISONERS AND THEIR OPPORTUNITIES

Prisoners at Wakefield are by no means a random sample: as a training prison it has for many years received either " star " class men (first offenders, usually about two-thirds of the total) or those thought particularly likely to benefit from the considerable opportunities there for vocational help. All classes of offence are represented, and recent overcrowding has obliged the authorities to admit men less likely to respond favourably; but disruptive prisoners are excluded when possible. Some 10%, with particularly clear psychiatric features, are picked out for psychotherapy. Training is offered to the 600-odd men in the various aspects of the building trade, carpentry, tailoring, farming, engineering, textiles, rug-making, and even iron-founding; and guild examinations are taken, usually with success. The prisoner has the added benefits of a generally easier life, longer periods of " association ", single cells, and greater opportunities to play games in the fairly generous space available. " Prisoner participation ", the informal meetings of leaders, and limited conduct of their own sporting and social affairs has been a growing feature of the Wakefield system since the 1920s.[1]

ORIGINS AND TECHNIQUE OF GROUP COUNSELLING

Dr. Alfred Torrie conducted group psychotherapy among the prisoners between 1953 and 1956, and at the same time several of the lay administrative staff took a lively interest in the sociological aspects of group interaction. The principal medical officer, Dr. W. F. Roper, also played a crucial part in the spread of the technique, through the introduction of systematic group discussions with prisoners as a part of the training of prospective assistant governors. Thus, although the psychiatrists now there no longer use formal group psychotherapy, group methods have spread into the routine conduct of prison affairs.

The extension to prisoners began some twelve months ago, and all intakes are now organised into groups of 8 to 12 men who, over one week, are introduced by a particular officer to prison life and its potentialities. This induction course includes sessions with the deputy governor and the

1. Report of the Commissioners of Prisons for the Year 1957; p. 29. H.M. Stationery Office. Cmnd. 496.

principal medical officer, who introduce them to the experience of free expression and to discussion of the role of authority in the prison. Over the next six months (or less if a man is posted to a special course), in addition to the usual prison life, groups meet weekly for an hour and a half with the same prison officer under informal conditions for discussion of anything and everything: the usual circle of chairs of the group I joined was on one of the lawns. The free-for-all at these sessions seems genuine enough, and most men are able after a short time to express their hostile feelings without fear of retribution, and there have been no abuses of this freedom—for example, in physical assault. The training of the prison officer in this technique is very brief—a short course lasting five days with emphasis rightly on non-intervention, to allow the men to answer each other's queries and doubts, and thus to found a group, rather than an authoritarian, approach to their difficulties. A ten-day pilot course has been started at the staff college for officers sent from other prisons. Six months seems to be the useful life of the group: partly, of course, because this period has become the accepted norm, but it may be because a group like this, if it is to continue longer, must delve more deeply. There is little or no dynamic interpretation and, although the technique clearly resembles group psychotherapy, the process is not deliberate "insight therapy". Experiences from early life, feelings towards early authority figures, and so on, arise occasionally, but such subjects apparently evoke much anxiety and are rapidly changed. Sex emerges more readily and is often discussed.

A rough content-analysis of documents relating to 7 sessions of one group (the 5th to the 11th), based on frequency and length of discussion, put the leading topics in the following order: (1) minor prison administrative detail, especially food; (2) relationship with authority in the prison; (3) problems related to discharge; (4) sexual problems; (5) problems related to the group situation, difficulty of speaking, &c.; (6) relations with the police, alleged brutality, &c.; and (7) distrust of prison companions.

The attitude towards lifers, capital punishment, and psychiatrists (cynical here) came in for brief mention, and conversation seemed spontaneous and wide. The onesidedness of prison organisation, and the apparent uselessness of any complaint of a prisoner against an officer, engendered a bitterness and hostility which were evidently a surprise to many of the administrative staff. Policy among the four wings (or "firms", each under an assistant governor) differed, and attendance was voluntary or compulsory, though response was notably better to voluntary schemes, so that all are now voluntary. Problems of technique and reports of progress with the 90 or so men in groups at any one time are discussed at weekly meetings attended by the officers conducting groups and by senior staff, but not by a medical man until very recently.

RESULTS

The change in prison atmosphere seems clear enough: there is a feeling of enthusiasm, even of fervour, among the officers doing this work and a feeling that this may be the most important thing to happen in penology for a very long time. Hierarchies are being broken down and the ease of relationships between men of different grades has to be seen to be believed within such a traditionally rigid and authoritarian service. The prisoner thus experiences a secondary effect—that of the overall change in administration and attitude—as well as the primary one through the interactions of his group. Here he has a ready approach to authority and an opportunity to voice grumbles: much tension is relieved which might otherwise be acted out violently and "incidents" in prison life seem to have been greatly reduced. Numbers absconding from Pollington Borstal, the other institution where these methods were pioneered, have also fallen off. Group methods have also helped to foster a more humane approach by the staff to the prisoner, and to create the "therapeutic atmosphere" which is essential if treatment of prisoners is to succeed. We must realise that to antagonise and intimidate a criminal still further is the very worst way to create a law-abiding citizen, and that, after all, is what matters most.

On the obverse side it is said that some more hardened men have exploited the laxer atmosphere and been disruptive, which was to be expected, since the sincerity of any change for the easier is bound to be put to the test. On the prison officers not so far included in the groups the effect has been interesting: there seems to have been a certain hostility, but too much should not be made of this—presumably it is analogous to the stimulant action on the "control" group excluded from certain benefits in a mental-hospital programme.[2]

PSYCHOTHERAPY OR COUNSELLING?

Despite clear similarities in technique, those concerned with counselling are anxious to avoid the term "psychotherapy", which suggests encroachment into psychiatry. Clearly there is a difference in depth and in aims, but to some the similarities may seem to be close. The perceptive prison officer will come to understand and use the transference relationship in which he is involved and to develop a deeper interest in the origins of deviant behaviour and, come to that, in the origins of his wish to become a prison officer which may be just as dynamically determined. It is not to be deplored that laymen are doing this work; for arising as it does from the prison service, and from the disciplinary side at that, it evokes less suspicion among the people who are making it work than it would, say, had it come from outside psychiatrists, who are generally looked on with doubt by both prisoners and staff. Again, where in the conceivable future could trained group psychotherapists be found to tackle more than a handful of our 25,000 prison population?

THE FUTURE

The need for experienced psychiatric advice may be crucial to further development, and some at least of the staff working with groups at Wakefield would welcome an expert adviser at their supervisory conferences, and this is now in fact in hand. Such help may be particularly important when counselling is extended to hard-core recidivist prisoners. The medical and lay techniques of treating deviant behaviour are likely to become closer, and it is in everyone's interest that they do so side-by-side rather than head-on.

The scientific evaluation of this vital experiment seems scarcely to be contemplated. Probably prison staff could not find the time for this task, and it is important too that those observing and reporting on this type of sociological experiment should not be bound up too intimately in it. The time to begin such observations, however, is the beginning and a precious chance of gaining important knowledge should not be lost. We need to know as clearly as possible the effects of what we are doing, in both the short and long term, in order to do better in the future; but the outlook for a service capable of throwing up a movement like group counselling must surely be very good indeed.

2. See *Lancet*, 1958, ii, 737.

GENERAL MEDICAL COUNCIL

SESSION NOV. 24

BEFORE Sir DAVID CAMPBELL'S presidential address (reported last week) Mr. Claude William Guillebaud, nominated for England and Wales by Her Majesty, with the advice of the Privy Council, for five years from Sept. 29, 1959, was introduced as a member of the Council, and was elected a member of the Disciplinary Committee.

Dr. GUY DAIN presented the report of the Pharmacopœia Committee, announcing that 27,796 copies of the *British Pharmacopœia* had been sold. The defence society which had acquired the adjacent premises formerly occupied by the General Dental Council had leased the upper floors so that the Pharmacopœia Commission could continue to occupy its present premises; the laboratories and rooms were being rearranged and re-equipped.

The Council approved simpler arrangements for a practitioner ordinarily resident outside the United Kingdom who wishes to have his name removed from the Register. On receipt of an application on a prescribed form, signed and witnessed, the President will be able (subject to reference to the executive committee of any application which appears to him to be questionable) to direct the Registrar to remove the name of the practitioner from the Register.

On the recommendation of the executive committee the Council agreed to direct the Registrar to remove the name of Mr. *Jeremias Auret van Heerden* (M.R.C.S. 1917, M.B. Lond. 1920). It was stated that Mr. van Heerden was resident in South Africa and was registered in the South African Register. He had made an application which failed to comply with the existing standing orders. He gave as one reason for his request the " multiplicity of medical circulars and advertisements " addressed to registered practitioners, even resident at a distance from this country.

Medical Disciplinary Committee

The committee met on Nov. 25-27, under the chairmanship of the President.

APPLICATIONS FOR RESTORATION

The Registrar was directed to restore to the Register the name of *Nicholas Freville* (formerly *Lupkovics*). The committee did not direct the Registrar to restore the name of *John Bodkin Adams*. It adjourned consideration of an application by *Robert Lindsay*.

REMOVAL FROM REGISTER

Kenneth Merrall Fox, registered as of Byways, Charleville Lane, Sonning, Berks, M.B. Leeds (1937), was charged with adultery with a married woman patient, in respect of which he was guilty of infamous conduct in a professional respect. Mr. G. J. K. Widgery, solicitor to the Council, said that the woman had committed suicide while the balance of her mind was disturbed.

Mr. N. Leigh Taylor, of Messrs. Hempsons, for the Medical Defence Union, objected to the admission of letters, one addressed to the British Medical Council, said to have been written by the dead woman and found in the room where she had taken an overdose of ' Seconal '. In the absence of the committee, he submitted that the committee should not receive the letters because its duty to make inquiry was no higher than that of a judge in a criminal court, who would not receive them; and it could have received the letters other than from the coroner and would have had no duty then to make inquiry, so that the letters themselves did not put that duty any higher. He also said that because they were written by someone found to have been of unsound mind they would be prejudicial. When Mr. Taylor said he wanted to refer to the contents, the Legal Assessor said the public should be excluded. The Press and public withdrew while the argument continued in the presence of the parties, the Legal Assessor, and the Registrar.

Subsequently the Legal Assessor said that it was obvious, he thought, that these letters, like any other letters written by anybody, threw some light—he would not say more than that—on the state of mind of the person when they were written. However, this was not an inquiry into the state of mind of the woman at the time she wrote the letters: it was an inquiry into whether Dr. Fox and the woman committed adultery together; and he had come to the conclusion that it was not desirable, in order that the committee might make due inquiry into that, that these letters should be before them, at any rate yet.

During the subsequent hearing a police stenographer produced a transcript of a telephone conversation between Dr. Fox and a witness.

The committee found the facts alleged against Dr. Fox proved to its satisfaction. It judged him to be guilty of infamous conduct in a professional respect in relation to the facts proved against him and directed the Registrar to remove from the Register the name of *Kenneth Merrall Fox*. This is subject to notice of appeal within twenty-eight days.

Edward John McCann, registered as of 96, Clyde Road, East Croydon, Surrey, L.R.C.P.I. (1948), was charged with having been convicted at Croydon Magistrates' Court in July, after pleading guilty, to fraudulent conversion and falsely pretending he was a person authorised to prescribe medicines under the National Health Service and, with intent to defraud, causing 50 ' Equanil ' tablets to be delivered to Doreen Mary McCann. There were three like offences of the second kind, and he had asked for sixteen similar cases of false pretences to be taken into consideration: he was fined three sums of £25 with the alternative of a month's imprisonment in each instance. There were two charges of fraudulent conversion, for which he was sentenced to two terms of three months' imprisonment, to run consecutively.

The committee ordered the erasure of the name of *Edward John McCann*, by reason of the convictions proved against him. He has twenty-eight days in which to appeal.

Francis Radcliffe How, registered as of c/o National Provincial Bank, Machynlleth, Montgomeryshire, M.R.C.S. (1927), was charged with being convicted at Tunbridge Wells Magistrates' Court in July on six charges of obtaining credit by fraud, for which he was sentenced to six months' imprisonment on each of the first two charges, the sentences to run consecutively, and to three months' imprisonment to run concurrently on each of the last four charges, and of obtaining credit by fraud, in respect of which he had been placed on probation by the same court in February and for which in July he was sentenced to one month's imprisonment to run concurrently with the other sentences.

The Registrar was directed to erase from the Register the name of *Francis Radcliffe How*. This is subject to appeal within twenty-eight days.

Liam O'Shea, registered as of 25, Whitacre Street, Deighton, Huddersfield, M.B. N.U.I. (1947), admitted convictions in 1948 and 1950 of being in charge of a motorcar when under the influence of drink. On the first occasion he was fined £10, ordered to pay £3 3*s*. costs, and disqualified for twelve months, on the second £15 with £3 3*s*. costs and disqualified for two years. He also admitted being convicted at Leeds Assizes on Dec. 16, 1958, of unlawfully using an instrument to procure a miscarriage and of conspiring with Mrs. Sheila Margaret Duquemin to procure this miscarriage, for which he was sentenced to three years' imprisonment, reduced, on appeal, to eighteen months.

By reason of the convictions, the Registrar was directed to erase the name of *Liam O'Shea*. He has twenty-eight days in which to appeal.

Robert George Mair, registered as of White Lodge, South Green, Billericay, Essex, M.B. Aberd. (1947), did not appear but sent a letter. When he was first summoned to appear before the committee in June, 1958, on a charge of conviction in 1947 of being drunk and disorderly, using obscene language, and causing wilful and malicious damage, and in January, 1958, of stealing £9 14*s*. in a dwelling-house, it was informed that he was unfit to plead. The inquiry has twice since been adjourned in view of evidence received as to the condition of the prisoner. Mr. Widgery said Dr. Mair was admitted to Runwell Hospital in January last year as a paranoid schizophrenic, but he absconded and therefore was discharged by the operation of law.

By reason of the convictions, which the committee found proved, the Registrar was ordered to erase the name of *Robert George Mair*. This is subject to appeal within twenty-eight days.

POSTPONED JUDGMENT

Henry Stanley Marshall Perera, provisionally registered as of St. Nicholas, Tudella, Jaela, Ceylon, L.R.C.P.E. (1959), was charged with having, whilst employed as a house-surgeon at Waveney Hospital, Ballymena, stolen £2 from the clothing of a professional colleague, in consequence of which he pleaded guilty to a charge under the Larceny Act at Ballymena Petty Sessions. The case was treated as one of infamous conduct in a professional respect because he was given a conditional discharge, which is not a conviction for the purpose of the committee's proceedings. The committee found the facts proved and judged Dr. Perera guilty of infamous conduct in a professional respect in relation to the facts proved. It postponed judgment for a year until November, 1960.

Geoffrey Roderick Richards, registered as of 5, Corrymore Mansions, Sketty Road, Swansea, M.R.C.S. (1937), who was not legally represented, was charged with: (1) on numerous occasions between Jan. 29 and March 3, 1959, unlawfully procuring for himself by means of National Health Service prescriptions made out in the names of various patients dangerous drugs, pleading guilty to twenty-five offences against the Dangerous Drugs Regulations at Dudley Magistrates' Court; and (2) calling for the purpose of attending a patient when he was under the influence of drugs to such an extent that his professional judgment was impaired. Dr. Richards had been put on probation on condition that he remained an inpatient at a hospital. The committee found the facts alleged in the first charge proved to its satisfaction, but decided that the second charge was not proved. It postponed judgment for one year.

Gerald Francis Adye-Curran, M.C., registered as of 4, Park Place, Liverpool 8, L.R.C.P.I. (1934), was sentenced to twelve months' imprisonment and disqualified from driving for life at Liverpool Assize for driving a motor-car when under the influence of drink. The committee postponed judgment for eighteen months, until May, 1961.

Richard Maurice Dooley, registered as of 74, Eglinton Road, Donnybrook, Dublin, M.B. Dubl. (1945), was charged with having been convicted at Thames Magistrates' Court in 1957 of being in charge of a car when under the influence of drink, when he was fined £50 and ordered to pay £5 costs with an alternative of three months' imprisonment and disqualified for twelve months; in April, 1959, at the same court of being drunk in a public place (fined 7*s*. 6*d*. with an alternative of seven days' imprisonment); and in June at the same court of being drunk and disorderly (10*s*.). Mr. Widgery said there was another conviction in May which had not been notified to the Council. The committee postponed judgment for one year.

Michael Ambrose Owen, registered as of 49, Bro-Deg, Cwmbach, Aberdare, Glamorgan, M.B. Wales (1951), was charged with convictions at Aberdare in 1958 of driving a motorcar under the influence of drink, when he was fined £15 and disqualified for twelve months, and on Aug. 19, 1959, of driving a motorcar in a dangerous manner, when he was fined £20 and disqualified for fifteen years. The committee postponed judgment for eighteen months, until May, 1961.

George Lewis Minter, registered as of 62, High Street, Haddington, East Lothian, M.B. Edin. (1950), admitted being convicted at Salford Magistrates' Court of stealing five cheques of the value of 10*d*., for which he was fined £50, one further offence of larceny being taken into consideration, and of obtaining by false pretences with intent to defraud a motorcar valued at £45, for which he was fined £50. The committee postponed judgment for one year, until November, 1960.

Florence Berchmans Lawlor, registered as of 50, Beaumont Street, London, W.1, M.B. N.U.I. (1936), challenged the accuracy of a charge that on May 27, 1959, at Bow Street Magistrates' Court he was convicted on four charges of obtaining dangerous drugs by false pretences contrary to the Larceny Act, for which he was sentenced to two months' imprisonment on each charge, the sentences to run concurrently: he pointed out that they were not dangerous drugs. Mr. Widgery was given permission to amend the charge. Dr. Lawlor had also been fined £15, ordered to pay £9 9*s*. costs, and disqualified from driving for twelve months in 1950 at Formby Magistrates' Court for being in charge of a motorcar when under the influence of drink. Mr. Widgery said there was another conviction in 1956 on four charges of failing to keep a record of dangerous drugs. The conviction was not referred to in the charge because his name was not on the Register, having been temporarily erased under section 14 of the Medical Act, 1958. His authority to prescribe dangerous drugs was withdrawn in 1956 and had not been restored. The committee postponed judgment for one year.

CASES CLOSED

The Registrar was not directed to erase the names of *Alfred Francon Williams*, registered as of 18, Crabtree Lane, Sheffield, 5, M.B. Edin. (1950); of *Josef Jan Labno*, registered as of 84, Claughton Road, Birkenhead, M.B. Polish School of Medicine (1943); of *George Thomas Alexander Hastings*, registered as of 142, Robin Hood Lane, Hall Green, Birmingham, 28, M.B. Glasg. (1929); and of *Patrick Francis MacDonald*, registered as of c/o A. MacDonald, solicitor, Main Street, Granard, Co. Longford, M.B. N.U.I. (1941).

Dialogues of Today

THE BEST-LAID PLANS?

SOCRATES: I believe, Erythro, that you are an advocate of State control. Why do you believe in that?

ERYTHRO: For two reasons, Socrates. In the first place, if people are left to act in what they believe to be their private interest there is no reason why this should be the interest of society as a whole, and it may well not be. The State, in self-preservation, therefore, must control the individual. The second reason is simply the complexity of society today. Assuming all individuals to be animated solely by altruism, even the largest industry hasn't the means to see how it can best play its part in relation to society as a whole, even within the nation, still less when it comes to international trade and finance. State planning is essential: the more complex the organism the greater its need for central coordination.

ERYXIMACHUS: Erythro suffers from the failing of all idealists, Socrates. He finds something wrong with the existing state of affairs. He proposes a remedy, which he finds good by contrast, and this blinds him to what is bad in the remedy, which may be worse than the disease. Coordination! Look what State control and planning have done for the Health Service.

SOCRATES: And what have they done?

ERYXIMACHUS: Diseases are not limited to individuals: society can suffer from them too, and sometimes the diseases of society strongly resemble those of individuals. For example, the Health Service exhibits the cardinal symptoms of a disease characterised by slowness of movement, rigidity, and tremor, and it seems to me that these are inherent in planning. No planner on the national scale can act quickly in a democratic society because any substantial change is like dropping a stone into a pond. Its ripples affect an ever-widening circle of interests, which have to be consulted, placated, or at least considered. And inevitably some will think it a bad thing, and no politician will do anything anyone thinks a bad thing if he can avoid it. And this creates the rigidity, for it is always easier not to change than to change, and minorities who object to change tend to carry more weight than majorities who want it. So rigidity in the Health Service is due to the same cause as it is in the human disease—increased resistance of mutually opposing muscle groups.

SOCRATES: And the tremor?

ERYXIMACHUS: That is the alternating movement which in its finer form occurs between the two sides of a committee, when it is known as "taking it back", while an ampler movement is seen in the oscillation from one committee to another with a rhythm of perhaps three or four movements a year. When this tremor becomes very severe it culminates in a state of complete immobilisation or catatonia lasting several years and known as a Royal Commission.

SOCRATES: And what happens then?

ERYXIMACHUS: If the question at issue is merely one of social ethics a state of apathy supervenes, which lasts indefinitely, and in which no action occurs: but if it is a matter of finance a convulsion is more probable.

ERYTHRO: There is something in what Eryximachus says, but what is the alternative? If there is no planning there is bound to be incoordination which he would perhaps understand better as ataxia. He puts the difficulties he describes down to planning, but I think they are really due to too little planning, or to planning of the wrong kind.

ENTHUSIASTICUS: I entirely agree, Socrates. I don't see any justification for calling the Health Service a planned service at all. There is very little more planning in it than there was in the old days of the voluntary hospitals. The same or similar people sit on the same or similar committees debating much the same things. The only difference is that any decision, from appointing a registrar to rebuilding a hospital, involves more people on more committees and takes much longer. But the Health Service, now running as planned twelve years ago, was then deliberately based on its structure of twenty years ago. No-one seems yet to have awakened to the fact that medicine itself has changed profoundly in the last twenty years, so that the structure of the Health Service is already out of date. Those committees which are not doing the routine day-to-day administration are trying to squeeze the living and growing body of medicine into the plaster cast of the past—the modern equivalent of the bed of Procrustes. What the Health Service is suffering from is in the strict sense of the term mental deficiency, exemplified in failure to grasp the meaning of complex situations, lack of foresight, and social irresponsibility.

SOCRATES: And who is to blame for that?

ERYXIMACHUS, ERYTHRO together: Erythro! Eryximachus!

ENTHUSIASTICUS: Human nature!

SOCRATES: It is I, I think, who must be to blame; for if, as you rightly say, the Health Service suffers from mental deficiency, those who think should have thought better, and taught others better, what is the nature of the good, and how it can best be attained; and you could then have applied those principles to medicine and its organisation. For government is surely the most difficult of all arts, and one which can be practised successfully only if those who govern have time also to think.

In England Now

A Running Commentary by Peripatetic Correspondents

ADVENTURE, it is said, happens only to those who seek it. What happened to me, then, was only a series of gentle incidents. That night, after a short professional trip two-thirds of the way across the North American continent, I waited at the airport for Flight 967 to take me home. Delays were repeatedly announced from the starting city of the plane and finally, an hour after scheduled time of departure, cancellation of the flight because of adverse local weather. Twelve hours later, I sat at lunch in another aircraft, still on the ground at the same airfield. Across the aisle, in the hands of a passenger, I saw a newspaper with the headline: PLANE CRASHES. For the first time, I knew why I had spent the night on the benches of the waiting-room. Coming in to pick me up, Flight 967 had crashed in the waters of the Gulf of Mexico; among those lost was a doctor who lived several miles from home.

The "lunch" plane never left the ground; no. 4 motor would not cease misbehaving. It was now Monday night and the bus raced from one Texas airport to another; the jealousies of the two adjacent cities had overruled the commonsense idea of a single terminal to serve them both. A mammoth jet liner waited; jet liners are speedy in the sky, but remarkably dilatory about leaving the ground. Identifying myself as a "967" survivor evoked a reaction best described as one of mingled revulsion (potential death) and awe (actual life), and I went aboard as the last "stand by".

Twenty minutes later, at 28,000 feet and more than 9 miles a minute, I heard "Are you a doctor?" I was. There was a woman who needed attention. She was young and exceedingly pregnant. Two days before, after an X-ray, she was told she was carrying twins in breech position. What was her expected day of delivery? Today. But, she assured me, the doctor had told her twins usually came a fortnight later. She added, however, that an hour before emplaning, she had fallen, striking her abdomen.

A bed of pillows was made on the floor near the galley. The uterus was not contracting and there was only localised tenderness in a rectus muscle below the ribs. All seemed well until she made repeated visits to the lavatory. She was not sure whether she was discharging urine or amniotic fluid. "You see, Doctor, with me the bag of waters never ruptures, it just oozes." She had not been pregnant for 8 years, and she had forgotten so much. A suggestion of mine and another visit to the lavatory: it was only urine.

I prepared a message of information and instructions for the plane's captain to be telephoned to the ground should labour set in. Psychotherapy, however, was effective. She said, "You know, you're the first doctor who ever took the trouble to sit down and talk to me, to explain things." Of course, she was my only patient; the other 125 passengers were not waiting to consult me.

We landed. Half an hour later, her relatives claimed her and I was free to drive home. Oh yes, my luggage was left behind in Texas.

* * *

Every year about this time our gardener presents us with a copy of *Old Moore's Almanack*, a work in which he has much faith, though as far as I can see it has not changed greatly in recent years. It was in the frank hope of furthering the sale of his pills that Dr. Francis Moore first published it two hundred and sixty-three years ago, and I must say that the edition for 1960 is just as uninhibited. In its pages are to be found remedies for disorders affecting almost every part of the body, literally from top (hair-restorer) to toe (my poor feet), although pills have disappeared. However, tablets have taken their place and the appeal, as in the days of Old Moore himself, remains chiefly feminine since the aim of therapy is to alter in one way or another the contours "above the belt" as the radio cliché has it.

Still, I learnt something new from the prophecies. It seems that the Kabalistic number for 1960 is 16, which is under the influence of the planet Mars, and as a result clashes will occur

between World Politicians, although happily they are to be resolved. As Osler said a long time ago, " credulity remains a permanent fact . . ."

* * *

The week before our visit we received a glossy descriptive brochure, with an impressive notice requiring our arrival by 12.30 promptly for a security check. Our sense of responsible citizenship thus suitably flattered, we ground over the mountain roads like men on some Wellsian adventure. With boiling radiators, we arrived promptly at the gates to find them locked, the place deserted, and no sound came save the wind howling dismally over the sea.

After some time we found an aged man sweeping up leaves, but he was too deaf to understand our problem. So we trundled despondently round the perimeter, and after two miles came upon another gate, against which was leaning a shortish gentleman whom we first took to be a character from the local production of *The Pirates of Penzance*, so long and flappy was his policeman's tunic. " Security check? " we asked. " Not at all," he replied, " lunch over there."

We were now on holy ground, and wondering vaguely about our strontium 90 uptake. We trooped into the Nissen hut as directed; at first we were cheerful despite the filthy washbasins and the total mechanical failure of the W.C., but our spirits sank rather when after forty minutes lunch turned out to be cold Irish stew. We were relieved to be rescued by a scientist and conducted to the inner sanctum; but our guide evidently had acute laryngitis, and what with this and the hum of machinery, we learnt remarkably little. During a three-hour tour, the only comprehensible item seen was a red knob, a touch on which " in case of emergency " would cause all the elements to fall out of the bottom of the reactor. This would involve the nation in an expenditure of several million pounds, and quite dwarfed the more common temptation to stop trains at £5 a time. The knob was heavily guarded by, no doubt, carefully selected personnel.

Cynicism deepened in the contamination detection department, for the hands, not only of our guide, but of all of us caused red lights to flash, and loud bells to ring; the Geiger counter was clearly unwell.

We had been much disturbed by an intermittent coughing noise coming from one of the machines; though reassured by our guide at the time, we felt justified when we read in the next day's paper that a flywheel had come loose, gone through the wall, and killed a neighbouring cow at a range of 600 yards.

* * *

Although I live within 4 miles of the Northern end of M.1, I have not ventured on it yet. " It's miles quicker to London," a lady told me, to which her husband pedantically replied, " And about 10 miles longer." Another friend who gets on near the start told me he did the 62 miles from there to London in fifty minutes without dropping below 60 and not going more than 75. As his average speed was 74·4 I believe he didn't have his eye on the speedometer all the while and for that I am grateful. On the first Sunday it was opened many boys from a nearby public school got their parents to take them for a spin along it. The first place after the start at the Northern end on which it is possible to join it is near Crick, and many thought they could get off here. However, they found they couldn't and had to carry on another 10–12 miles to Weedon before they could turn back. The number late for Chapel that day was a record. This goes to prove that the advice is sound: " Don't go on the M.1 unless you have studied the map."

* * *

NO PARKING

In Kensington and Curzon Street
The cop now pounds a lonely beat
And in the dusk, along Park Lane
Philanderers may stroll in vain
For London's streets are simon-pure;
Each social evil has its cure
And London for its Past atones
With Red Lights dimmed to mere Pink Zones.

Letters to the Editor

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—The late Wilfred Trotter once said: " The most powerful antigen known to man is a new idea." It is therefore with some interest that I have recently watched in your pages the mobilisation of antibodies to an idea put forward by my colleagues and me some years ago. The new idea is that essential hypertension represents a quantitative deviation from the norm; the old idea is that the deviation is qualitative. The evidence against the new idea and in favour of the old has been advanced by Platt and by Morrison and Morris (Nov. 21). You comment: " We find this new evidence that essential hypertension is a specific disease both convincing and more in keeping with its clinical behaviour."

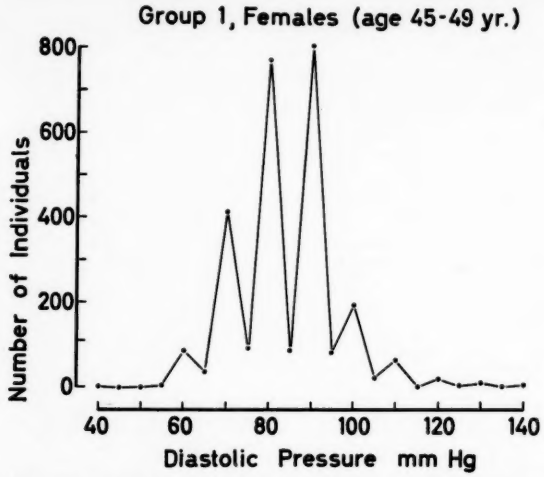
Before your readers are overwhelmed by the present reaction of immunity may I suggest a few reasons why they should at least consider the quantitative idea seriously.

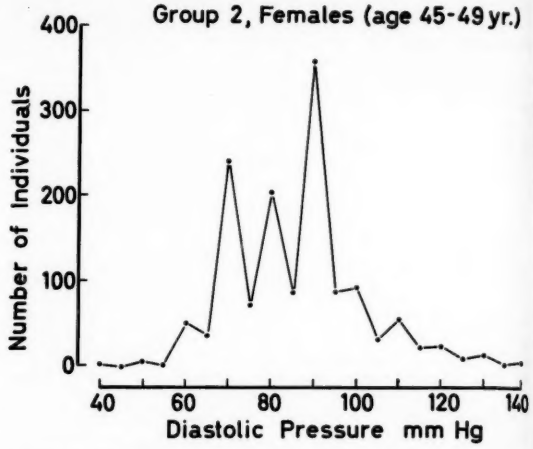
Let me first correct one impression. Morrison and Morris attribute the quantitative idea to me. The exact parentage of a new idea is often difficult, and always invidious, to trace. Hamilton, Roberts, Sowry, and I sought to seek better evidence concerning the genetics of essential hypertension. In planning our work we tacitly accepted the old idea of a qualitative difference between normal blood-pressure and essential hypertension, and the provisional hypothesis that inheritance was that of a mendelian dominant gene. The new idea that blood-pressure was inherited as a graded character dawned, and steadily became more convincing, when it became apparent that there was a quantitative relationship between the deviations from the norm of the arterial pressures of our patients with essential hypertension and those of their first-degree relatives, and that however the degree of resemblance between hypertensive propositi and their relatives was calculated the regression coefficient always came out at a little over 0·2. While then I cannot accept more than my share of credit for the new idea, I admit I have been perhaps its most ardent exponent. To understand high blood-pressure, why it develops and what it does, has been my chief obsession over the past thirty-five years. And I have to confess that the new idea makes sense to me, while the old was one with which my mind was never really comfortable. It is just for this reason that I should not like to see the new idea rejected without a word being said in its defence.

The evidence for the old idea is bifid distribution curves —that is to say, curves with two peaks. Now this can happen by chance, particularly when numbers are small; to this cause may probably be attributed the curves of Morrison and Morris's fig. 8 giving the age of death of fathers in Platt and Sobye's patients with essential hypertension, for it is to be noted that the trough in Platt's series is at age 65, the same age at which Sobye's reaches its peak. But there are also technical reasons why distribution curves may not be smooth.

The accompanying figures are the frequency distribution curves for diastolic pressure for females aged 45 to 49 of the population of Bergen, Norway (Boe, Humerfelt, and Wedervang [1]). Blood-pressure was measured in 67,976 persons. Group 1 was examined from January to June, 1950, and group 2 in January to May, 1951. " The pressure was read to the nearest 5 mm. " Now it will be seen that both curves show a conspicuous predominance of figures ending in 0. This phenomenon is common in surveys of this kind, is probably to

1. *Acta med. scand.* 1957, **157**, suppl. 321.





be correlated with our arithmetic being based on the decimal system, and is termed by statisticians "unconscious digit preference". This kind of result is particularly likely to occur if readings are made to the nearest 5 mm., a practice which we also unfortunately used. Even if 0s and 5s are combined, fig. 2 shows in addition a bifid curve with a deficiency of readings at 80 mm. Hg. This deficiency at 80 mm. was present at every age-group from 15–19 to 45–49 in both males and females of the second sample. It was never fully explained but there seems little doubt that these bifid curves were due to the same kind of unconscious digit preference. Platt remarks in his paper [2]: "It is interesting that the main dip in the curve occurs at about 150/90, which is exactly the figure most commonly chosen by clinicians as the dividing line between normal and high blood-pressure in middle-aged subjects." The question arises whether the dip could have arisen from unconscious digit preference. This question may never be finally answered, but it seems fair comment to remark that both Sobye and we ourselves in making the measurement that Platt used for his curves had one question in mind: "Have the relatives got hypertension or have they not?"

Let me suggest some reasons why the new hypothesis should not be rejected forthwith.

(1) Biometrically and genetically speaking it makes sense. Francis Galton [3] showed seventy years ago that human stature was inherited as a graded character and remarked that this was just what would have been expected, since stature depended on the sum of the sizes of a number of different structures. In the same way arterial pressure is the resultant of a large number of variables. If we accept the one-gene/one-enzyme hypothesis what is likely to be the biochemical lesion in essential hypertension? This is no idle issue because I am one who has devoted more years than I care to remember trying to find just that, a specific and unique cause—fruitlessly as it happens, though some fascinating problems have turned up on the way.

(2) The evidence that arterial pressure is inherited as a graded character is really rather convincing. Our evidence has been mentioned. However, the strongest evidence is that of Miall and Oldham [4] who showed that in a random sample of the population of the Rhondda Fach and the Vale of Glamorgan, the deviations from the norm of arterial pressure propositi were quantitatively related to the deviations of their first-degree relatives, and this relationship was the same over the whole range of pressure. The relationship of relatives and subjects having the lowest pressures was qualitatively exactly the same as we had found between relatives and subjects with so-called essential hypertension. I find it extremely difficult to believe that this relationship between propositi and relatives is due to chance or to bias. It has been suggested that this is an artefact due to the method of scoring, but it should be remembered that Galton, while finding a similar relationship for height, had also to use a device for adjusting the values measured, since females are shorter than males.

(3) If one looks at the effects of hypertension the relationship between them and blood-pressure is also quantitative. The evidence is collected in my book *High Blood Pressure*. I find it hard to believe that even those who believe "the evidence that essential hypertension is a specific disease . . . more in keeping with its clinical behaviour" consider that there is no difference between an arterial pressure of 160 and one of 260, or that the disparity between them is not greater in every way than between pressures of 140 and 160. Yet if one accepts the hypothesis for which the clinical behaviour is said to be so strong this is not so; 140 is normal and 160 and 260 are both abnormal.

(4) Platt's hypothesis of the nature of the specific genetic difference between normal blood-pressure and essential hypertension implied that rise of pressure with age is a feature of the latter but not of the former. On this point the evidence is fairly conclusive. The rates of rise of arterial pressure with age in our first-degree relatives of subjects with essential hypertension did not differ significantly (more than the 5% level) from those of the relatives of patients without hypertension or from those of the population sample except for systolic pressure in males.

These remarks are not meant in any way to constitute a rebuttal of the evidence submitted by Platt and Morrison and Morris. This evidence is being seriously considered, and our own reviewed by Roberts, Sowry, Oldham, and myself, with the possibility clearly in mind that the hypothesis for which we are responsible may require modification or extension. The purpose of this letter is to suggest that your readers should examine the evidence as a whole before the predicted immune reaction has totally rejected the new idea.

Oxford. G. W. PICKERING.

SIR,—Dr. Morrison and Professor Morris have demonstrated a bimodal distribution in the systolic blood-pressures of those London busmen who said that one or both of their parents had died between the ages of 40 and 64. They argue that high blood-pressure must have been commoner among this group of parents than among those who lived longer. With this one must probably agree. They then deduce that the finding of bimodality in the distribution of the offsprings' systolic pressure is evidence for the inheritance of hypertension by a single dominant gene. This conclusion may or may not be true; but it certainly cannot be proved from this evidence.

2. *Lancet*, July 25, 1959, p. 55.
3. Natural Inheritance. London, 1889.
4. *Clin. Sci.* 1955, **14**, 459; *ibid.* 1958, **17**, 409.

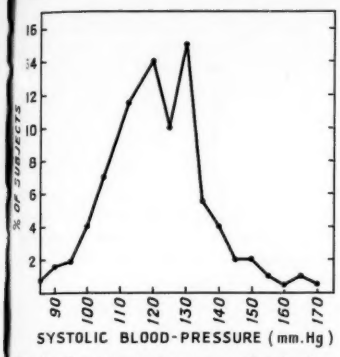


Fig. 1—Combined frequency distribution in the children of (a) 180 parents with high diastolic pressures and of (b) an equal number of parents, matched for age, with normal diastolic pressures.

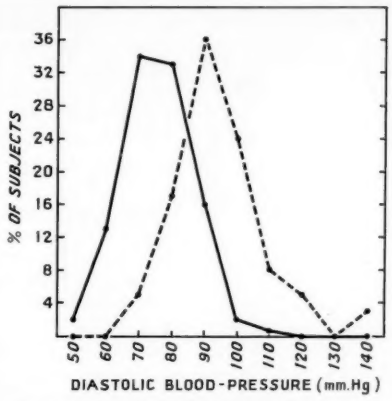


Fig. 3—Result of dividing fig. 2 into those with systolic pressures of 160 mm. or more and those below 160.

The parents who died in middle-age comprised two groups: those (an unknown number) who died because they had high blood-pressure, and those who died from other causes. The pressures of the first group would be distributed about a high mean, whereas those of the second group would be distributed probably about the same mean as the general population. In other words, the blood-pressure distribution of these parents is likely to have been bimodal. From this it follows that the finding of bimodality in the next generation is evidence for a familial resemblance in blood-pressure, but tells us nothing of its mechanism.

To test the validity of this criticism we have used the data of Hamilton et al.[1] and Miall and Oldham [2] to study the systolic blood-pressure distribution in the children of (*a*) 180 parents with high diastolic pressures, and (*b*) an equal number of parents, matched for age, with normal diastolic pressures. These parents are comparable to the (supposedly) hypertensive group of bus drivers' parents. Not surprisingly, the systolic pressures of the two groups of children are distributed about separate means, and the combined frequency distribution curve of the two groups (fig. 1) is bimodal. This simply confirms that a bimodal distribution of a heritable characteristic tends to be transmitted from one generation to the next.

1. Hamilton, M., Pickering, G. W., Roberts, J. A. F., Sowry, G. S. C. *Clin. Sci.* 1954, **13**, 273.
2. Miall, W. E., Oldham, P. D. *ibid.* 1955, **14**, 459.

Fig. 2—Frequency distribution of 200 systolic blood-pressure readings from homogenous population group.

When they examined the distribution of diastolic pressures, Dr. Morrison and Professor Morris found no sign of bimodality. They proceeded to divide their subjects up into two groups, the one composed of those with systolic blood-pressures of 160 mm. or more, the other of those with lower pressures. This procedure, they point out, unmasks two distinct components to the distribution curves of diastolic pressure. They infer that this is further evidence in support of their thesis.

We have carried out the same manœuvre for a series of 200 blood-pressure readings taken from a homogeneous population group, whose systolic pressures (fig. 2) showed a unimodal distribution. This procedure again unmasks two distinct components to the distribution curves of diastolic pressure (fig. 3). The only conclusion we would draw is that a correlation exists between a man's systolic and diastolic pressures.

St. Mary's Hospital, London, W.2.

HARRY KEEN
GEOFFREY ROSE.

SIR,—Platt [1] and more recently Dr. Morrison and Professor Morris have published examinations of the distributions of arterial pressures in selected populations and claim to show that such distributions are usually bimodal and reflect the division of people into two groups characterisable as normotensive and hypertensive. This claim is in contradiction of an earlier finding of Hamilton and his colleagues [2] that pressures were unimodally distributed and that the distributions shifted towards higher pressures as successive age-groups from 10 years to over 80 years were examined. Morrison and Morris claim that the apparent increase in pressure with advancing age is due to the increasingly more frequent finding of hypertensive patients and they provide other evidence which they submit is suggestive that hypertension is a distinct disease entity determined probably by a single dominant gene. Hamilton and his colleagues have proposed that the evidence of their inquiry is more consistent with the view that hypertension is polygenically inherited in a manner similar to the mechanisms of inheritance postulated for height or intelligence.

It may be instructive to deduce some of the relevant consequences of the two hypotheses.

Examination of the distribution of pressures in successive age-groups in the data published by Hamilton et al. shows that the distribution moves towards the higher pressures in successively older groups. The shift is such that in the 70-and-over age-groups 81% of females and 50% of males have systolic pressures of 160 mm. Hg or over and 46% of females and 36% of males have diastolic pressures of 95 mm. Hg or over. If these observations relate to a group of people exhibiting a distinct disease determined by a dominant gene we must suppose that carriers of the gene have a frequency varying between 36% and 81% according to the criteria adopted. Further, this frequency must be a minimum frequency for carriers since it seems unlikely that persons bearing the gene

1. Platt, R. *Lancet*, 1959, July 25, p. 55.
2. Hamilton, M., Pickering, G. W., Fraser Roberts, J. A., Sowry, G. S. C. *Clin. Sci.* 1954, **13**, 11.

are favoured in respect of survival when compared with those who do not carry it.

If these assumptions are accepted, the gene frequency must be somewhere between 30% and 50%. If we accept the data of Morrison and Morris on age at death of fathers of " hypertensives " as indicating the lethal effect of the gene for hypertension, we must assume that it results in a curtailment of life expectation amounting to some 10 to 15 years as compared with the general population. It seems surprising that the effect of a gene at once so common and so lethal has never previously been observed.

The hypothesis advanced by Hamilton and his colleagues that essential hypertension represents the upper end of a distribution of pressures owing its variability to the effect of a polygenic system would in general involve the assumption that parents, sibs, and offspring of persons with high arterial pressures would on average exhibit pressures between the mean population value and that for propositi. The distribution, however, would be expected to be unimodal. Platt[1], using data of Hamilton et al.[3] has shown sibs of propositi to be bimodally distributed with respect to arterial pressures and assumes that the two modes represent the segregation of a dominant gene within fraternities selected by the presence of one affected member. If this explanation is correct it seems surprising that the modal value in the higher of the two peaks is so much lower than the modal value for the propositi. In fact the modal value for the higher peak would appear to be about 170 mm. Hg systolic pressure compared with 220 mm. Hg for the propositi. The lower peak has a modal value broadly similar to that in the general population at around 135 mm. Hg. A similar finding is observed in the case of diastolic pressures where the mean value for propositi aged 40–60 is 130 mm. Hg being considerably higher than the modal value in the higher peak among sibs (110 mm. Hg).

It seems then that sibs of hypertensive propositi fall into two distinct groups. One group has an arterial pressure distribution similar to that of the general population and the other group has a pressure distribution falling between that of the general population and that of the propositi.

It seems that a further hypothesis is now required to account for the data on record. One which leaps readily to mind is that hypertensive individuals may be divisible into two groups. One group consists of individuals whose hypertension is not inherited or at least is not simply due to a single dominant gene substitution. The other group whose sibs have pressures between that of the general population and that of the propositi represent the upper end of a distribution of pressures owing its variability to the effects of a polygenic system. It may well be that in only one of these groups do pressures usually increase with advancing age. It is interesting that the distributions of pressures among propositi from the data of Hamilton et al. show some evidence of bimodality.

An acceptable hypothesis should be able to account for the findings of Morrison and Morris that fathers of hypertensive subjects have bimodally distributed ages at death, and that sons of parents who died in middle age have bimodally distributed arterial pressures. A hypothesis which divides essential hypertension into two categories of which one is not inherited and the other is can satisfactorily accommodate these findings without postulating any specific mode of inheritance.

Department of Public Health
and Social Medicine,
Queen's College,
Dundee. ALWYN SMITH.

3. Hamilton, M., Pickering, G. W., Fraser Roberts, J. A., Sowry, G. S. C. *ibid.* p. 273.

TRAINING OF DENTAL AUXILIARIES

SIR,—The General Dental Council is inviting applications for the post of director of the first school for training dental auxiliaries ever to be set up in this country. It is to be opened in October, 1960.

By means of this entirely new and experimental approach to the problem of the acute shortage of National Health dentists, the Government will launch partly trained young persons, after a specially shortened course, into dental practice in an attempt to fill the alarming and ever-increasing gaps in the ranks of fully trained general dental practitioners.

After more than 11 years of Government management and absolute control of National Health dentistry, the public, who after all are chiefly concerned in this experiment, may wonder why dentistry has become so unpopular and unattractive that standards of education have had to be drastically reduced so that an entirely new kind of auxiliary dentist may be created to attend to them instead of fully trained ones.

The General Dental
Practitioners Association,
London, N.1. H. RANSOME MARKHAM
General Secretary.

EXPERIMENTAL LATHYRISM IN THE ALBINO RAT

SIR,—Your leader of Oct. 3 discussed my paper, among others, on the mechanism of scoliosis. There is something to be added.

The development of scoliosis was found to be but *an incident* during the conversion of the kyphosis into lordosis. The rat possesses physiologically a cervicodorsal lordosis ending at the 2nd or 3rd thoracic vertebra. From there on to the last coccygeal vertebra a marked kyphosis is present. The conversion of the kyphosis into lordosis begins very soon after the administration of sweetpea. It comprises the entire thoracic, lumbar, sacral, even slightly the coccygeal region. Yet one, sometimes two, sites in the thoracic spine not only maintain their kyphosis but increase it to a veritable gibbus. During the development of lordosis the spine penetrates the posterior mediastinum and the posterior abdominal cavity. This forward movement hardly could take place exactly in the strict sagittal plane since the ribs and vertebræ became soft; so the spine deviates also to the right or to the left side, and scoliosis develops.

Scoliosis is situated invariably in the regions which underwent lordotic conversion, never in the remnants of the kyphosis or in the physiologically lordotic part. The mechanism of conversion is the main factor, not the lordosis itself. The disruption of the epiphyses seems to play a subordinate role, if any, in experimental scoliosis while it is the essential trait of habitual scoliosis of the dorsal spine, as shown in my former studies.

The development of pathological lordosis has been traced by me to several factors. One of them is the bilateral compression of the thorax through the pressure of the forelimbs creating pathological thorax deformities, which I termed " redoubling " of the thorax. Another is the pressure of the scapulæ, and probably the frequently paradoxical respiration. More important is the traction exerted by the thoracic and abdominal viscera hanging down and pulling the spine by their weight.

I chiefly blamed the penetration of the spine into the mediastinum for the development of aneurysms, for the enlargement of the heart, the venous congestion, and eventually for the sudden rupture of the vessels accompanied by hæmothorax and sudden death.

It is emphasised in the paper that almost identical conditions prevail in scoliosis accompanying rickets, but even habitual scoliosis shows the decrease or complete disappearance of the dorsal kyphosis during the course of development. Also another analogy was found. Human scoliosis is also accom-

panied by enlargement of the heart, venous congestion, even by aneurysms, and sudden death may occur at an early age.

In order to delay the penetration of the spine into the mediastinum in my second experimental series, at the start of feeding sweetpea, the clavicles were removed. At this point the animals were three weeks old. It was hoped to delay also the progress of scoliosis by the intervention.

In my second experiment 10 animals were used. It is worth mentioning that 4 of them, all females, were still alive at the age of 25 weeks, while in my former experiment comprising 32 animals, and also in that of others, almost none of the animals was alive after 10 weeks of feeding sweetpea. So it was concluded that the excision of the clavicles, despite the progress of lordosis, relieved the mediastinum of the fatal pressure.

The question naturally arises whether the excision of one or both clavicles in the human, a rather simple and harmless procedure, might not be attempted in circulatory disturbances similar to those in the experimental animal. The more so as the clavicles become thickened and enlarged, the sterno-clavicular discs degenerate, the soft tissues grow more rigid at and around the bone with advancing years.

If the clavicles represent one of the sources of ischæmia, and of venous-lymphatic congestion in or around the mediastinum, a number of conditions could benefit from the intervention, such as the thoracic-outlet syndrome, aneurysm, coarctation of the aorta, even coronary conditions, among others. Their partial or total removal from the path of the gradually impeded circulation might be considered.

New York Medical College,
New York, N.Y. ALADÁR FARKAS.

THE ÆTIOLOGY OF LEUKÆMIAS

SIR,—Dr. Murray's contention (Oct. 17) that "the new thought that will find the cure for leukæmia must clarify the biochemical derangement in precise terms" surely overlooks "chance and the absence of thought"! Is it not a fact that South American Indians unversed in pharmacology, chemistry, bacteriology, and public health controlled attacks of malaria with Peruvian bark long before quinine, the malarial parasite, and the anopheles mosquito were stated in these precise terms?

Cape Town. M. GLASS.

ADAPTATION IN CALCIUM ABSORPTION

SIR,—At the end of your annotation of Nov. 7 it is suggested that patients who are in negative calcium balance will develop osteoporosis. Surely there is no direct experimental or clinical evidence upon which to base this supposition?

Although Nordin [1] maintained that a negative calcium balance might prove to be a factor in the causation of this disorder, he also pointed out that there had been little work to substantiate this and made it clear that he suggested this mechanism to discourage unreserved acceptance of Albright's theory that a dysfunction of the matrix is responsible.

Comparison of the histology of decalcification and osteoporosis makes it difficult to accept that calcium depletion alone will result in osteoporosis. Decalcification of bone is recognisable by a failure of deposition of bone salts in the osteoid matrix which in turn results in the classical wide calcified osteoid seams; this is associated with a normal or increased degree of osteoblastic activity. Osteoporosis shows no such evidence of decalcification but there is a gross reduction in the number of osteoblasts lining the trabeculæ, a totally different picture. The changes in the bone are similar, whether the osteoporosis is associated with severe burns, septicæmia, or steroid therapy.

Whilst it is accepted that such an atrophy of the bone matrix is associated with an increased calcium excretion and negative balance, it does not follow that because a patient is in negative balance the cellular component of bone should be affected. It is also of interest to note that van Buchem [2] suggested that osteoporosis *and* osteomalacia may develop after prolonged steroid therapy—i.e., two quite distinct pathological entities in the same bone, one the result of a disorder of bone matrix, the other due to increased excretion of calcium.

It is agreed that the generally unsatisfactory response of osteoporotic patients to anabolic steroids indicates that the present conception of hormonal influence is unlikely to be correct, yet it seems equally unlikely that negative calcium balance is any more than a secondary manifestation in osteoporosis.

Department of Physical Medicine,
Guy's Hospital, London, S.E.1. P. HUME KENDALL.

CATION-EXCHANGE RESINS IN ACUTE RENAL FAILURE

SIR,—In your annotation of Sept. 19 you write, "... a resin completely charged with sodium, (this) being ineffective by enema" and also "resins charged with hydrogen ion would be much more potent in hyperkalæmia where treatment by enema is indicated." I cannot agree with these statements if they mean that a sodium-cycle resin alone does not remove potassium ions from the lower colon. In-vitro experiments, the ability to elute large amounts of potassium from sodium-cycle resins returned by colonic lavage, and clinical experience all suggest that the sodium salt of carboxylic-acid type resin will remove potassium from the lower bowel:

The following is a typical case-history to demonstrate this point.

A married woman, aged 46 years, was admitted with a diagnosis of malignant hypertension and uræmia. At 9 A.M. serum-electrolytes were potassium 6·5, sodium 128, chloride 81, and bicarbonate 17 mEq. per l. The non-protein nitrogen (N.P.N.) was 203 mg. per 100 ml. and the hæmoglobin 5·8 g. per 100 ml. During the subsequent 24 hours the patient excreted 75 ml. of urine and did not vomit, whilst the fluid intake consisted of 1 litre of 5% dextrose in saline solution and 200 ml. packed red cells intravenously.

At 4.15 P.M. an electrocardiogram was reported as: "Abnormal. P waves cannot be identified but the ventricular rhythm is regular. Since previous tracing an intraventricular block of the right bundle-branch type has developed. The changes are compatible with high blood-potassium."

Between 6 P.M. and 9 A.M. next morning, 120 g. sodium-cycle carboxylic-acid-type resin were given by retention enemas (24 g. 4-hourly), all except a portion of the first enema being retained. After the last treatment the serum-electrolytes were potassium 5·4, sodium 129, chloride 84, bicarbonate 18 mEq. per l., and the N.P.N. was 204 mg. per 100 ml. An E.C.G. was reported as "Abnormal, the rhythm is now sinus (i.e., P waves can again be identified) and the right bundle-branch block pattern noted on previous tracing is no longer present. The pattern is now non-specific and is compatible with lowering of the blood-potassium since previous tracing done 13 hours ago."

The serum-potassium concentration and E.C.G. pattern were maintained for the subsequent 24 hours by 96 g. of sodium-cycle resin in spite of a urine output of only 90 ml. and a further transfusion of packed red blood cells. The patient died next day.

During the time when this patient was receiving sodium-cycle carboxylic-acid-type resins the serum-potassium level was lowered and electrocardiographic changes compatible with hyperkalæmia were improved. This occurred in spite of a urine secretion of only 165 ml.

1. Nordin, B. E. C. *Brit. med. J.* 1958, i, 1415.

2. van Buchem, F. S. P. *Brit. med. J.* 1959, i, 933.

and no other visible losses. During this time the patient received 1300 ml. of fluid intravenously, 300 ml. of this being in the form of packed red cells which might be expected to have released some potassium.

My thanks are due to Dr. D. S. Munroe for permission to quote this case.

Department of Pathology,
Vancouver General Hospital,
Vancouver, British Columbia. J. EDEN.

ACUTE ANOXIC CARDIAC FAILURE IN PULMONARY HEART-DISEASE

SIR,—Dr. Kellaway's excellent paper of Nov. 7 recalls my own experience in general practice during the "great smog" of December, 1952.

No cases were sent to hospital. Patients were nursed in a room with a large open fire with a good chimney draught to ensure adequate ventilation and warmth. Windows and doors were kept shut and covered day and night, with thick curtains, or other suitable material, to minimise the entry of smog particles.

Oxygen was given by the standard polyethylene mask whenever dyspnœa was apparent. Usually five to ten minutes inhalation would relieve dyspnœa for about two hours.

Nikethamide was given parenterally in an initial dose of 2 ml., followed by 20 minims orally every two hours. In addition to its action on the respiratory centre, nikethamide by its central and peripheral vasopressor action raises the systemic blood-pressure, thus tending to restore the pressure gradient in the thebesian vessels and hence the carriage of oxygen to the right myocardium.[1] No antibiotics were given, since the cause of the dyspnœa was clearly exudation caused by a chemical irritant in the smog. Non-productive cough was relieved when necessary by diamorphine, which was still available at the time. This also tended to diminish shallow breathing by "damping" the oversensitive Hering-Breuer reflex.

There were 8 patients with advanced chronic (non-tubercular) chest disease, all with very severe dyspnœa and pale cyanosis. All survived the smog and none developed bronchopneumonia.

London, S.E.13. ALLAN CHATELIER.

RISKS ASSOCIATED WITH ELECTROPLEXY

SIR,—Dr. Rahill (Nov. 14) complains that I did not deal with two points he raised.

I deplore particularly the growing tendency in many hospitals for the complicated time-consuming and expensive modified technique to be applied to all patients treated with electroplexy. It is depressing too to find that this is usually regarded as a progressive policy. If the efficiency and safety of ectonus were more widely recognised I believe that in most centres it would be found better to give ectonus to more than 90% of the list and use modified E.C.T. for less than 10%.

My own statistics regarding fractures are 1 fracture of neck of femur in a patient aged 60-odd in just over 4000 individual doses of ectonus personally given since September, 1956. All the patients to whom I give ectonus are concurrently having a course of a phenothiazine drug and almost all are given ectonus intensively—i.e., one daily dose until a confusional state develops.

I wish to state emphatically that in my experience ectonus is *not* an unpleasant treatment from the patient's point of view. After the first dose patients typically return cheerfully for subsequent doses. Many of them report so favourably that one finds other patients asking whether they can have the treatment.

I do not agree with Dr. Rahill when he says "E.C.T. is still E.C.T. no matter what name it is given or which type of apparatus is used". Indeed it would be an advantage to limit the use of "E.C.T." so that it refers only to the traditional or "one-shot" method in which clonic convulsions are prominent. (The ectonus technique represents a successful attempt to find a *non*-convulsant form of electrotherapy.) If this is done it is easier to avoid the error of assuming that principles established in regard to E.C.T. and lessons learned in the clinical use of it have validity for any form of electrotherapy which may develop subsequently to E.C.T. Experience with ectonus has provided much evidence to the contrary. This could, for example, be illustrated by considering Dr. Rahill's statement that fractures caused by E.C.T. occur mostly in the tonic phase. I assume this to be correct. But if it is implied that it logically follows that fractures are a specially serious risk with ectonus, I do not agree, despite the fact that ectonus produces a sustained tonic seizure. The tonic phase in E.C.T. is sudden and jerking in onset. With ectonus its onset is slower and smoother.

Dr. Rahill mentions "a considerable body of opinion against giving patients E.C.T. every day". I agree, but only because I use E.C.T. in a narrower sense than he does. When applying electrotherapy intensively I use ectonus. A few psychiatrists, I believe, use E.C.T. intensively in the treatment of acute mania. Otherwise the only people in this country who are able to speak from experience of the intensive use of electrotherapy are the orthodox users of ectonus and its forerunner "fused dosage".

Fear of brain damage must in the past have deterred many therapists from using active physical treatment and denied recoveries to many patients. I have found no evidence of brain damage with intensive ectonus, but instead many recoveries, usually accompanied by improved physical health.

Lennox Castle,
Lennoxtown. ALLAN A. MACDOUGALL.

SELECTION AT CELLULAR LEVEL AND THE ECOLOGY OF TUMOURS

SIR,—I can accept the spirit of Dr. Loxton's assurances (Oct. 3) that the ecological aspects of tumour ætiology have been explored, but I am not confident that I succeeded in making the point I wished to. Perhaps you will allow me one more short attempt.

Accepting that there are two environments, one outside and one inside, and attempting to disentangle their respective influences upon the evolutionary process, it seems to me that function derives from outside and has no primary valency relative to the internal environment. On those lines I would regard cell differentiation as purely metabolic and I would regard intercellular relationships as being parallel to the relationships which maintain the balances between outside species. Pursuing that approach leads one to conclude that differentiation in the two environments has a parallel ecological basis and in fact that the only relevant difference lies in the actual mechanical method by which it is achieved.

Cell differentiation reaches the embryo as a gene which is related to one particular biochemical competence that will remain dormant in the gene-complex of the cell until such time as it is evocated. The evocator is part of the cell's environment but the competence is part of the cell's heredity. Clearly then, the environmental evocation of a competence does not involve the grossly Lamarckian creation of a gene, and one could if one were grudging about it dismiss the situation as being merely quasi-Lamarckian. With rather better grace, one could accept that the genetic status of the differentiated cell is an elegant example of truly Lamarckian inheritance. Such graciousness is well worth while because it affords the opportunity of appreciating the elegantly Darwinian nature of intercellular relationships generally.

Without wishing to be in any way dogmatic, I suggest that there is no absolute necessity to invoke the relatively clumsy conception of differential survival to account for the attainment of the tumour cell's only really essential attribute—namely, its ability to achieve and maintain local dominance. I do not wish to propound yet another cancer theory but I have no objection at all to suggesting that what we do require is an adequate theory of evolution that would embrace the whole subject comfortably.

1. Myers G. N. *J. Hyg., Camb.* 1940, **40**, 474.

May I thank you, Sir, for affording me the space in your columns to broach a subject, the unintended defence of Lamarck, which is a long way short of being fashionable. The only excuse which I can offer is the conviction that the occasional reversibility of some tumours, and the fact that some sites appear to attract metastases while other sites appear to repel them, and so on and so on, really do exculpate the tumour cell's genes, and really do incriminate the tumour cell's environment.

Colchester. MICHAEL FROST.

DOMICILIARY REHABILITATION OF THE RESPIRATORY CRIPPLE

SIR,—Mr. Capener (Oct. 24) might like to know that some of these patients are being cared for at home. In our practice we have a man of 26, who has virtually no movement except of his head and neck. He can "frog-breathe" for up to three hours but otherwise needs a Tunnicliffe respirator and pump. He is cared for very satisfactorily at home, and Rush Green Hospital, Romford, Poliomyelitis Unit is prepared to (and does) take him in at a moment's notice, if, for instance, he gets a cold.

We have been more fortunate than Dr. McKendrick (Nov. 14), as we have had excellent cooperation from all concerned. The County Health Department provide a special nurse; the local council have altered the house; the G.P.O. installed a telephone within 24 hours; the next-door neighbour services the pump; and the Association for the Physically Handicapped have helped in many ways. Rush Green Hospital, Romford, provided the Tunnicliffe jacket, pump, and Oxford hand bellows; and their ambulance (which can carry a tank respirator, if needed) is always used, although they come from outside our area.

Writtle, Essex. JOHN C. GRAVES.

REFORM OF THE LAW ON HOMOSEXUALITY

SIR,—I do not propose to reply at any length to Sir Heneage Ogilvie's letter of Nov. 21 as he seems to know as little about the problems of the homosexual as he does about the recommendations of the Wolfenden committee. Their report no more recommended that adult homosexuals should be left free to corrupt boys than that adult heterosexuals should be left free to seduce young girls. After reading Sir Heneage Ogilvie's letter I am left wondering whether he has ever met a homosexual and discussed his problems with him. If this letter is representative of the views of surgeons, then it is indeed fortunate that the Wolfenden committee was "overloaded with the views of psychologists".

London, W.1. KENNETH WALKER.

SIR,—Correspondence on homosexuality regularly produces a crop of assertions on either side which are quite unsupported by medical evidence, but rarely do you print such a misstatement as Sir Heneage Ogilvie's accusation that the Wolfenden committee ignored the views of "schoolmasters, scout leaders, and wardens of boys' clubs".

Pages 152–155 of that report list all the witnesses, and, except for an association representing the staffs of approved schools, who, as we have recently been reminded, are not schoolmasters in the usual sense of the term, and the legal adviser to the Boy Scouts Association, who is hardly likely to have given evidence as to the effect on scouts themselves, none of the witnesses is shown as speaking as, or on behalf of, the three groups named by Sir Heneage. The committee cannot be accused of ignoring evidence which was never tendered to them.

Dogmatic statements that professions hold this view or that seem out of place in this discussion: even if a poll were held, it is difficult to see that the work or training of the ordinary priest or doctor gives members of those professions any special qualification to pronounce on the social effects of homosexuality.

What is needed is a practical index of national corrosion. This would enable us, firstly, to measure the effect, if any, of homosexual behaviour in the process, and, secondly, the effects for better or worse of permissive and restrictive legislation. The former can be studied in such countries as France, Belgium, and Sweden, the latter here and in the U.S.A. and Western Germany.

Meantime, in liberal countries the onus lies always with the prosecution where there is a possibility of social injustice, and accordingly it seems reasonable to lay the burden of proof of harm on anti-Wolfenden alarmists.

Droitwich, Worcestershire. J. F. TUTHILL.

FOLIC-ACID DEFICIENCY IN PREGNANCY

SIR,—Dr. Chanarin and his colleagues (Oct. 24) are to be congratulated on their most elegant and comprehensive study of the mechanism underlying the production of megaloblastic anæmia of pregnancy. It is apparent from their work that of the factors involved fœtal requirement is probably the most important but impaired gastrointestinal absorption and deficient dietary intake may also contribute.

It has been claimed [1] that this type of pregnancy anæmia can be prevented by giving routine hæmatinic supplements including folic acid to pregnant women, and the work of Dr. Chanarin and his colleagues would seem to confirm the logic of this approach. It is, however, not one which has been generally favoured by clinicians in this country.

In one year we missed the diagnosis of megaloblastic anæmia in 5 cases with consequences potentially dangerous to the patients. Since then we have given folic acid in addition to iron to all pregnant women with any tendency to develop pathological anæmia—the indication being a hæmoglobin level of less than 80% (11·8 g. per 100 ml.). Approximately 10,000 pregnant patients have been cared for since this routine was introduced. Marrow puncture was not performed in these cases. None of these patients has developed serious anæmia (other than post-hæmorrhagic) and there has been no known case of relapse in the puerperium on stopping treatment.

Our reasons for adopting this policy are several:

(1) Folic-acid deficiency is common in pregnant women, and they are given free supplies of other vitamins much less vital to their health.

(2) Iron and folic-acid deficiency tend to occur in the same poorly nourished pregnant patients. 75% of Forshaw's [2] pregnant women with folic-acid-deficiency anæmia were also iron-deficient. Initial administration of iron alone may result in a temporary improvement in the hæmoglobin level. If folic acid also is deficient, megaloblastic arrest of hæmopoiesis will eventually occur but will often not be manifest clinically until the pregnancy is near term.

It is probable that for an area such as ours with a population of relatively poor nutritional standard, the true incidence of megaloblastic anæmia is even greater than the 1 in 39 quoted by Giles and Shuttleworth.[3] Our total incidence of pregnancy anæmia by the standards mentioned is of the order of 1 in 8.

(3) Folic-acid deficiency may be responsible for anæmia without the marrow being frankly megaloblastic. We have had several cases of iron-resistant anæmia in which the marrow has been reported normoblastic until both the pregnancy and the anæmia were dangerously advanced. Indeed, many false-

1. Lowenstein, L., Pick, C., Philpott, N. *Amer. J. Obstet. Gynec.* 1955, **70**, 1309.
2. Forshaw, J. W. B. *Postgrad. med. J.* 1958, **34**, 222.
3. Giles, C., Shuttleworth, E. *Lancet*, 1958, ii, 1341.

negative reports are to be expected if the investigation consists of a single marrow puncture reported by a single observer. Forshaw [2 4] did a great service by admitting that in a previous study [5] the diagnosis had probably been missed in 2 out of 3 cases, and this in a unit where the condition was the subject of particular interest.

(4) Economically this policy is very worth while. The cost of one month's supply of ferrous gluconate (gr. 5 t.d.s.) and folic acid (5 mg. t.d.s.) is covered by the prescription charge, and if ferrous sulphate is given rather than the gluconate, the cost is more than covered. Admission to hospital for marrow puncture and for intensive treatment is unnecessary, and the considerable cost of blood-transfusion, which is needed if severe megaloblastic anæmia is diagnosed late in pregnancy, is also saved.

(5) The fear of giving folic acid to a case of addisonian anæmia is probably the main reason why folic acid is usually withheld until marrow puncture has been performed. This is unreasonable, for marrow examination has little to contribute to the differential diagnosis. Nor do tests for gastric acidity help, since approximately 30% of cases of folic-acid-deficiency megaloblastic anæmia show achlorhydria. Serum-vitamin-B_{12} estimation is the only investigation likely to prove helpful.

It should, of course, be a rule in all cases of pregnancy anæmia to stop therapy after the immediate postpartum period and to check that relapse does not occur. Fortunately the incidence of addisonian anæmia in pregnancy is extremely low, and neither Giles and Shuttleworth nor Forshaw had any cases which relapsed with cessation of treatment.

In dealing with deficiency states—and pregnancy anæmia is clearly such a state—specificity of therapy is not desirable, while prevention is very much better than cure.

Department of Obstetrics and Gynæcology, University of Liverpool.
H. H. FRANCIS
J. S. SCOTT.

COLORIMETRIC ESTIMATION OF 3-METHOXY-4-HYDROXYMANDELIC ACID IN URINE

SIR,—We recently described a quantitative colorimetric method for the estimation of 3-methoxy-4-hydroxymandelic acid (V.M.A.) in urine.[6] This procedure, in which V.M.A. is separated by passage through a column of Dowex 1x2 anion exchange resin (200–400 mesh) and then converted to vanillin, is quite satisfactory for the diagnosis of phæochromocytoma. It tends, however, to give excretion values in normal subjects which are appreciably higher than those obtained by chromatographic [7] or electrophoretic methods.[8]

Certain modifications in our technique have now been instituted which give a normal range in much closer agreement with that obtained by other workers. We feel that these modifications affect the method sufficiently to require an interim report, prior to definitive publication.

(1) *Ethyl acetate.*—Some samples of ethyl acetate AR contain an unknown labile impurity which gives rise to a variable interfering colour. We now use "ethyl acetate (B.D.H., special for spectroscopy)" which is satisfactory; but as an added precaution we carry out procedures 2 and 3 also.

(2) *Column blank.*—We run 1 ml. of water through the entire procedure with every set of estimations. The calculation is therefore amended to

$$\frac{\text{Test—Column blank}}{\text{Standard—Standard blank}} \times 8{\cdot}15$$

(3) *Evaporation at higher temperature.*—Instead of removing the ethyl acetate at 40°C, we now do this at 60–70°C also under vacuum.

(4) *Conversion to vanillin.*—Instead of employing 5% v/v sulphuric acid, we autoclave with 2% v/v hydrochloric acid which is also used for the vanillin standard and standard blank. This is the most important single modification.

(5) *Final colour.*—This is read at 3 min.

Using this revised procedure we have obtained a mean excretion and standard deviation of the mean for young adults of $6{\cdot}1 \pm 0{\cdot}7$ mg. V.M.A. per 24 hours.

The Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Maternity Hospital, London, W.6.
M. SANDLER
C. R. J. RUTHVEN.

4. Forshaw, J. W. B. *Lancet*, 1959, i, 101.
5. Forshaw, J. W. B., Jones, A. T., Chisholm, W. N., McGinley, W. K. *J. Obstet. Gynæc. Brit. Emp.* 1957, **64**, 255.
6. Sandler, M., Ruthven, C. R. J. *Lancet*, Aug. 15, 1959, p. 114.
7. Armstrong, M. D., McMillan, A. *Fed. Proc.* 1957, **16**, 146.
8. von Studnitz, W., Hanson, A. *Lancet*, Oct. 31, 1959, p. 736.

FACIAL FLUSHING IN CARCINOID SYNDROME

SIR,—I was interested to see in the report of Professor Peart and his colleagues (Oct. 31) that injection of adrenaline, noradrenaline, and 5-H.T. produced deep breathing followed within a few seconds by the typical carcinoid flush. This reminded me of a puzzling observation I had made in a patient with biopsy-proven carcinoid. The easiest way to produce a flushing attack was by having the patient breathe deeply a few times and, after a few seconds' delay, she would have a generalised flush. I first noticed this reaction during a routine stethoscopic examination of her lungs and was able to reproduce it repeatedly. Each time, she was in a standing position and the reaction was not easily produced if she were sitting.

I report this as an interesting observation but the mechanism is obscure to me.

Belmont, Mass. VASILIOS G. LETSOU.

TOLBUTAMIDE CONTROL OF DIABETES MELLITUS

SIR,—We wish to thank Dr. Murray for his apposite comments (Oct. 24) on our paper of Oct. 17.

We would agree that sulphonylurea therapy should not be used in the obese patient as a substitute for the more basic weight reduction. We use this treatment in such patients only when our persuasive capacity has failed to make them diet—i.e., when our first choice in treatment fails we move to the next choice, rather than give no treatment.

Our results have not suggested either much effect of the sulphonylurea treatment on the course of the obesity, or much effect on the obesity from the sulphonylurea treatment, provided one considers only non-ketotic diabetics. We also analysed the relevance of obesity to tolbutamide responsiveness. At the start of the trial we assessed as obese 4 of our 24 "good" and 2 of our 9 "fair" responders; during the trial only two of these changed more than 4 lb. in weight, one gained 14 lb. and one lost 16 lb. The patient's weight at the onset of the diabetes had also been assessed against that at 21 years as "normal". This data was obtained for 37 out of 38 patients in groups 1, 2, 3. While 8 were 10–30 lb. above "normal", and 4 were 30–70 lb. above "normal", the remaining 25 patients were "normal" or "under normal". Again no correlation was obvious between obesity and tolbutamide responsiveness as some have suggested.

Our findings also agree with Dr. Murray's that increasing the dose of tolbutamide beyond the $1^1/_2$ to 2 g. per day does not have any benefit and we now use only our standard dosage of 0·5 g. q.d.s.

We have never encountered danger in withdrawing insulin for 48 hours in suitable patients; but they must be suitably chosen. This is done only when our records show no history of ketosis (i.e., that is not very likely), the patient needs 40 or less units of insulin per day, and the patient has received satisfactory instructions about urine tests and the need to report if a strong ketone test is found.

Postgraduate Medical School, London, W.12.
G. F. JOPLIN
RUSSELL FRASER
J. VALLANCE-OWEN.

STAPHYLOCOCCAL CROSS-INFECTION IN SURGERY

SIR,—I read with interest the article of Nov. 7 by Dr. Gillespie and his colleagues. They found after one year that disinfection of blankets, pillows, crockery, cutlery, and baths, the frequent replacement of towels, and the intelligent use of antiseptics reduced the incidence of infection. In congratulating them on this result, I would point out that such practices have been routine in fever hospitals for many years, and that it might benefit everyone if nurses (and doctors for that matter) could visit or be seconded to fever units, where they could learn the application of these principles. I submit, Sir, that the fever hospital is the only place where this can be done satisfactorily.

Chadwell Heath Hospital, Romford, Essex — I. M. LIBRACH.

PRECORDIAL CATCH

SIR,—For several years I have been speculating on the cause of the " precordial catch ". I have been subject to it severely, perhaps ten times a year for at least fifteen years. There are no obvious precipitating causes, though it occurs usually while standing, and never while lying down. It corresponds otherwise closely to the description of Texidor and Miller.

I had often wondered if it might be due to local spasm of intercostal muscles, continually irritated by the apex beat, since it occurs exactly over this point. Later I discovered that I can often reproduce the pain, less severe, but worse on inspiration, by firm pressure upwards under the *right* costal margin, and also by pressure over the lower right ribs. This suggests that the pain may be related to the liver, perhaps to traction on the left triangular ligament. This would match the observation that it occurs more commonly when standing, the weight of the liver pulling on the ligament.

It is widely believed that spasm of the splenic flexure can produce referred pain in the chest. It seems possible that " the catch " might be a manifestation of this; its character suggests transient muscle spasm, and this is difficult to reconcile with traction on a ligament, unless this induces local left diaphragmatic spasm near its attachment. Pressure in the right hypochondrium might be transmitted through the transverse colon to the splenic flexure, but if this were the origin of the pain, why is there none on pressure at other points over the transverse colon?

Can anyone raise further evidence in my case against the liver?

St. Andrew's Hospital, London, E.3. — B. M. KING.

RECORDING CASES OF CANCER

SIR,—In your issue of Nov. 14, you published a review of *Malignant Disease, University College Hospital, 1946-50* in which you apply the adjective " herculean " to the task here recorded, and then brush off the book as one which might interest an archivist ".

It would be a pity if as a result of that remark, those about the country who are doing their best in difficult circumstances to implement the endeavour of the Registrar General to secure a nation-wide record of cases of cancer related to the whole population, were dissuaded from studying it. True it deals only with cases seen at U.C.H., but it records every case seen over five years, and if it did no more it would enable every member of that staff to compare his own results with those of his colleagues and ascertain whether he was giving as good a service to patients as he might. Wherever good records are being kept, that sort of inquiry is met with and help is readily forthcoming.

You lament the absence of " results ", " findings ", or " conclusions ". In fact the result, to date, of every case is recorded. Whether any single hospital, or even any single cancer bureau, should attempt its own statistical analysis or leave that to the General Register Office, is open to question, but no honest endeavour to make an objective record of every case dealt with should be treated with disdain.

E. ROCK CARLING
Chairman, Advisory Committee on Medical Nomenclature and Statistics, Somerset House.

IMPROVING THE ACTION OF ANTIHÆMOPHILIC GLOBULIN AND CHRISTMAS FACTOR

SIR,—Recent studies by Nour-Eldin and Wilkinson [1] have indicated that, in addition to the deficiency of antihæmophilic globulin and Christmas factor in hæmophilia and Christmas disease respectively, the clotting defect comprises the presence of a blood-clotting inhibitor termed Bridge anticoagulant. The latter was found to be responsible for the large amounts of antihæmophilic globulin required in the treatment of these patients.[2] It was, therefore, thought that should the action of this inhibitor be removed or neutralised, it would be possible to obtain the same improvement in the clotting defect by using a relatively small amount of anti-hæmophilic globulin or Christmas factor—i.e., the action of these clotting factors would be improved. The benefit achieved by doing so would be twofold: (*a*) the attainment of a proper physiological correction of the clotting defect in these diseases; and (*b*) easing of the difficulty now encountered in obtaining adequate supplies of blood and antihæmophilic globulin for the 2000 patients in this country.

With this aim in view, efforts were concentrated towards further studies on the behaviour of this anticoagulant. Its concentration during blood coagulation was found to remain constant until the formation of fibrin, whereupon a sudden decrease was noticed. No trace was found in serum 5 minutes after coagulation.

Experiments on the effect of different types of defibrination on the anticoagulant activity indicated that a substance derived from thrombin-fibrinogen interaction was capable of neutralising Bridge anticoagulant.

By investigating its properties, it is now possible to prepare this material called Bridge anticoagulant neutralising agent (B.A.N.A.) from pooled expired plasma, supplies of which should prove adequate for clinical trials. In-vitro experiments (see table) have demonstrated a great improvement in the formation of plasma-thromboplastin on incorporating B.A.N.A. solution (which is free of A.H.G.) in an incubation mixture containing undiluted * hæmophilic plasma (Bridge anticoagulant).

Substance incorporated in incubation mixture *	*Substrate clotting time (sec.)*†
0·9% NaCl (control)	27½
B.A.N.A. solution	14

* Equal volumes of undiluted $Al(OH_3)$-treated plasma, imidazole buffer pH 7·3, 1 : 10 normal serum, platelet suspension, 1 : 5 normal $Al(OH)_3$-treated plasma (source of A.H.G.), and 0·05*M* $CaCl_2$.

† After 6 min. at 37°C, 0·1 ml. of the incubation mixture was added together with 0·1 ml. 0·025*M* $CaCl_2$ to 0·1 ml. normal plasma (substrate), recording the clotting-time.

The Royal Infirmary, Manchester. — F. NOUR-ELDIN.

1. Nour-Eldin, F., Wilkinson, J. F. *Brit. J. Hæmat.* 1958, **4**, 38; *Lancet*, 1959, i, 1173.
2. Nour-Eldin, F., Wilkinson, J. F. *ibid.* p. 292.

CHRISTMAS FACTOR IN THROMBOTEST

SIR,—Dr. Nour-Eldin (Nov. 21) states that animal-brain extract (which is one component of the thrombotest reagent) "is known to contain Christmas-factor activity",[1] and "Accordingly, it seems impossible that the plasma clotting-times would be influenced by variations in the concentration of this factor".

The fact is that the thrombotest *is* sensitive to variations in the concentration of Christmas-factor activity (see fig. 4 on p. 755 in my paper of Nov. 7). Whenever a theory contradicts a fact, the theory is likely to be wrong. So also in this case. Brain extract definitely does *not* contain Christmas factor. In the experiments referred to,[1] Nour-Eldin has substituted tissue thromboplastin for platelets in the thromboplastin generation test of Biggs and Douglas.[2] The method thereby has been changed from being a test of the intrinsic coagulation system to a test of the extrinsic system (since the serum reagent contains proconvertin or factor 7). Consequently, his results do not allow any conclusions regarding A.H.G., Christmas factor, and platelets (see fig. 1, p. 754). It is well known that tissue thromboplastin acts independently of the antihæmophilic factors, but it is a mistake to translate this phenomenon to mean that tissue thromboplastin *contains* these factors.

The explanation why thrombotest is sensitive to variations in the concentration of Christmas factor is simple enough. Hæmophilic plasma gives a prolonged thromboplastin time with a dilute tissue thromboplastin,[3] and the same is found with a weak tissue thromboplastin. Waaler [4] showed that this was due to a simultaneous contribution to the formation of thrombin by the intrinsic and extrinsic blood-clotting systems under these circumstances.

Rikshospitalet, Oslo. P. A. OWREN.

CLINICAL STAGING FOR BREAST CANCER

SIR,—In your annotation of Nov. 28 your argument runs:

(i) "Clinical staging is suitable . . . in those sites where the primary lesion and its areas of spread are readily revealed."

(ii) "the extent of breast cancer can be assessed in all cases even without operation."

You continue that, owing to the presence of invaded lymph-nodes which cannot be detected clinically, "histological examination may not always support the clinical assessment". This obviously invalidates your argument unless you can show, either that such undetected invaded lymph-nodes are rare, or that their existence does not matter. Your statement that "this" (i.e., the presence of undetected invaded lymph-nodes) "matters little since treatment is selected in the light of the clinical, and not the pathological, findings" is irrelevant to the argument, which is concerned with the validity of "clinical staging" in the comparison of one case of breast cancer with another.

London, W.1. DAVID H. PATEY.

ANKARA CATS

SIR,—In his letter of Sept. 19, Dr. Smithells repeats a partial fallacy in his mention of deafness in long-haired white cats. The cat he describes is presumably the variety well known in the cat fancy as the odd-eyed white long-hair, which has one orange and one blue eye. These cats occur from time to time in litters from crosses between blue- and orange-eyed cats.

Bamber [1] has reviewed the claims that the blue-eyed white cat (the length of hair is irrelevant) is always deaf and that the condition is congenital. Further, the odd-eyed cat is supposed to be deaf on the side of the blue eye, but not on the other side. An examination of the possible mechanism of this condition has been published by Wolff.[2]

However, the number of scientific studies of this problem is very few, and the opinion of Bamber and many breeders of the blue (and odd) eyed variety of white cat is that these animals are by no means all deaf. I suggest that much more detailed study is required before any reported deafness of "Ankara" cats is accepted as applicable in medical research.

Sydney, New South Wales. G. G. ALLEN.

DIRT IN HOSPITALS

SIR,—Much has been said and written about dirt on hospital walls. Dr. Avery Jones [3] is obviously right in demanding its elimination even although bacteriological culture of the dirt seldom yields staphylococci. Hospitals have a duty to set an example of cleanliness before the community and to encourage their staffs to work towards this ideal, but one aspect of the problem seems to me not to have received the attention it deserves.

In Canada and the United States emphasis is laid on the necessity to reduce to a minimum maintenance costs even at the expense of considerable outlay in labour-saving devices. It is generally agreed that plastic surfaces, though dearer than painted ones, are infinitely easier and cheaper to keep clean. It is, therefore, somewhat depressing that in this country additions to hospital buildings are still being built with painted walls. Is this being done because the grants are too small to allow of the differences in cost or have years of parsimony inculcated in the planners the idea of painted walls so firmly that they cannot change? This short-sighted policy may be being encouraged by the authority responsible for providing the building not being the authority responsible for its maintenance later. One can only hope that the larger allocation recently announced will allow this policy to be reversed.

Central Middlesex Hospital, London, N.W.10. J. D. ALLAN GRAY.

ASSOCIATION OF FRIENDS OF POLISH PATIENTS

SIR,—Despite modern treatments and all the care and attention which are given to them, there still remain some 1400 Polish patients in mental hospitals in this country. This Association, since 1954, has each year provided an individual parcel at Christmas time for all these patients. This has been made possible by the kindness and generosity of the British public who have responded to our appeal. Each parcel costs 5s. All the work of packing and dispatching is done by voluntary helpers, so that donations received are fully expended on the patients. We appeal to all British families who are looking forward to a happy Christmas in their own homes to ask themselves how many parcels they can provide for these distressed and lonely people. We know from the letters we receive from the hospital superintendents that in past years our Christmas parcels have been felt by the patients to be friendly hands stretched out in the darkness. Let us not fail them in 1959.

Association of Friends of Polish Patients, 14, Collingham Gardens, London, S.W.5. BRIDGET MONCKTON OF BRENCHLEY.

1. Nour-Eldin, F. Fourth International Congress of Biochemistry. Vienna, 1958; p. 138.
2. Biggs, R., Douglas, A. S. *J. clin. Path.* 1953. **6**, 23.
3. Biggs, R., Macfarlane, R. G. *ibid.* 1951, **4**, 445.
4. Waaler, B. A. *Scand. J. clin. Lab. Invest.* 1957, **9**, 322.

1. Bamber, R. C. *J. Genet.* 1933, **27**, 407.
2. Wolff, D. *J. Hered.* 1942, **33**, 39.
3. *Lancet*, 1959, i, 203.

Parliament

Guidance or Control?

Mr. DEREK WALKER-SMITH, the Minister of Health, said that Parliament had several times interested themselves in providing an appropriate professional structure for callings which contributed to the well-being of the nation. In the Professions Supplementary to Medicine Bill they were doing this on an unprecedented scale, for 30,000 people and eight professions. The fact that there were eight professions (chiropodists, dietitians, medical laboratory technicians, occupational therapists, physiotherapists, radiographers, remedial gymnasts, and speech therapists) not linked in any common organisation was one reason why it had taken rather long to bring the Bill before Parliament.

In most schemes of this sort three main interests had to be borne in mind—the general public, the already qualified practitioner, and the practitioner without degree or certificate whose only qualification was his practical expertise. In this Bill there was a fourth interest to consider—the medical profession. The members of the supplementary professions had specialised skills either in the performance of diagnostic tests or in carrying out particular forms of treatment, but general management must remain a medical responsibility, however completely parts of it might be delegated. These considerations had necessarily complicated the formulation of the scheme, but he believed that the end-product satisfied alike tests of fairness and practicality.

Though the Bill was intended to make it possible to distinguish people eligible for employment in the public service, it did not seek to ban the employment of other than registered people. The desired result could be achieved either by administrative means or by making regulations under existing powers—e.g., the powers in Section 66 of the National Health Service Act. Nor did the Bill prohibit private practice by unregistered people: it merely protected the title "State-registered".

Mr. Walker-Smith had received a letter from the Speech Therapists' Association asking him to receive a deputation to discuss the suggestion that the Bill should not, after all, apply to them. He hoped that in the event the speech therapists would agree that there need be no conflict between statutory registration and appropriate academic courses, and would remain in the Bill. Representatives of the other professions had met at the Ministry and were substantially in agreement with the Bill. The medical profession took the view that there should be either equality of representation between doctors and the supplementary professions on the boards, or that the coordinating Council should have overriding powers. He had not been able to meet either of those requests; but he had strengthened the provisions in the Bill relating to the Privy Council, which should in another way meet the points that the medical profession had in mind.

Dr. EDITH SUMMERSKILL thought that the fears of the medical profession about their limited representation on the proposed boards and Council were unfounded, and that the medical profession should look forward to giving a helping hand to the men and women in the younger professions whose skill and industry were so helpful to the doctors and so beneficial to the public.

Sir HUGH LINSTEAD agreed that the Bill would work, if it was to work at all, not on a rigid numerical basis of representation, but on the basis that doctors wanted to help the professions and that the professions recognised their position in relation to the medical profession. The Bill was trying to set these professions on their statutory feet and to give them an opportunity to develop their own future. By and large, that could be done only if they felt that they were mistress in their own house, under the guidance of doctors but not under their direct control.

Dr. BARNETT STROSS also thought that the medical profession could only harm itself by making excessive demands on organisations similar to its own. He hoped that all these eight bodies, including the speech therapists, would remain in the Bill and he was delighted that the Minister had left the door open for others to come in.

Dame IRENE WARD was perturbed that the speech therapists should have found themselves included in the Bill without having agreed that they should appear.

Mr. R. H. TURTON recalled that the Bill had carried the prenatal title of Medical Auxiliaries Bill. He seemed still to be dissatisfied with the present version and suggested that it could more pleasingly be called the Healthy Professions Bill. (Mr. KENNETH ROBINSON later suggested the "Paramedical Professions".)

Sir MALCOLM STODDART-SCOTT pointed out that the medical profession was legally responsible for the action of all these auxiliaries. As well as being responsible for their actions, the doctors were to a great extent responsible for their education, and they wished to be well represented on the boards and on the Council. They had a parity on the Council only if the representative from the General Medical Council was a doctor. He hoped an amendment could be made to the effect that the General Medical Council should send a medical representative. The radiographers' board, he continued, was to have four medical representatives from the colleges and Scottish corporations. He hoped that it could be ensured that some of these medical representatives knew something about radiography and radiology, and it might be better to look for representatives to the Faculty of Radiologists and the British Institute of Radiology.

Mr. KENNETH ROBINSON was doubtful whether in law doctors were responsible for the action of these auxiliaries. He asked why almoners had been excluded from the Bill. He thought the objections of the speech therapists at least merited careful reconsideration of their case. He recalled that they had already withdrawn from the N.H.S. Whitley machinery and formed their own professional organisation which was now negotiating with the local education authorities before the Sudbury Committee.

The Bill conformed to a trend in the health services which he welcomed—increasing attention and emphasis to training on many fronts. It was hoped soon to see action on the report of the Younghusband Working Party on Social Workers. The General Nursing Council had recently reappraised nurse training. An investigation into administrative staffs by Sir Noel Hall laid stress on training to provide a proper career structure. But in the most important field of all, the medical field, there was little or no sign of any rethinking on training at all. Medical curricula were not basically different from those of half a century ago. The medical student was still taught within the strait jacket of what one might call the mechanistic theory of disease. He was taught all about the body, but nothing about the mind. At present the teaching on psychiatry was cursory in the extreme, yet mental patients occupied 48% of our hospital beds. There was no sign that the leadership of the medical profession would do anything about this without some stimulus from outside. Had not the time now come for a Royal Commission or some other kind of high-powered inquiry into medical education?

Miss EDITH PITT, parliamentary secretary to the Ministry, said that the debate had emphasised what the Bill's title implied—that the prime responsibility for these professions rested with the doctors, and that, though part of the treatment or care might be delegated to members of the supplementary professions, it was essential that it should remain under the control and general supervision of medical practitioners, though doctors were not responsible in law for what supplementaries did. The British Medical Association had thought that there should be equal numbers on the boards or that the coordinating Council should have overriding powers. But the medical auxiliary bodies had rejected these suggestions almost unanimously. In the circumstances, the Government decided that the proper solution would be to leave the supplementary professions with a majority of one on each of the registration boards and to leave the Council without overriding powers, but to provide that decisions on certain matters, in particular

courses of training and qualifications, should be subject to the final approval of the Privy Council.

Miss Pitt explained that, in the discussions leading to the preparation of the Bill, the view of the almoners was generally accepted—that they belonged to the field of social work, and had no real connection with auxiliaries or the supplementary professions. They had accordingly dropped out of the scene.

Disposal of Radioactive Wastes

IN the House of Lords the Radioactive Substances Bill [1] was given a second reading on Nov. 24.

Viscount HAILSHAM said the Bill proceeded on three principles: national control for the discharge of radioactive waste substances as distinct from local control: control in two tiers or storeys (control of users by registration and control of accumulation or disposal by authorisation); and provision for a national disposal service.

Describing the Bill as a sound piece of gas-and-water Socialism to delight the hearts of all old Fabians, Lord TAYLOR referred to the adsorption of radioactive material on to particles of mud in the sea bed or river bed. It seemed that more research was needed to make sure that harm was not being done by such adsorption, which might also occur in sewer pipes. It seemed, at a first reading, that the Bill virtually prohibited water authorities from taking any notice of the radioactivity of discharges from sewage works which they were found to receive. There were two different kinds of monitoring: simple monitoring to estimate the quantity of radioactivity; and qualitative monitoring to identify the radioactive substances involved. The first was easy, the second difficult.

Viscount HAILSHAM said that adsorption into mud was already the subject of a special study by the Water Pollution Laboratory. Water authorities were entitled to undertake monitoring, and they did in fact do so.

QUESTION TIME

Drugs for Private Patients

Mr. JOHN HALL asked the Minister of Health what representations he had received from the British Medical Association on the provision of drugs for private patients under the National Health Service; and what his reply had been to these representations. Dr. DONALD JOHNSON asked the Minister what was the nature of the administrative difficulties that prevent the provision of drugs to private patients under the National Health Service.—Mr. DEREK WALKER-SMITH replied: The British Medical Association has represented that drugs should be supplied to private patients on the same terms as to National Health Service patients. This raises considerations wider than those of administration.

Mr. HALL: Is the Minister aware that his predecessors in office stonewalled on this question for a number of years, first on the ground of cost, then on the ground that certain safeguards were necessary? Now that the profession has agreed to all the safeguards required, the Minister finds another reason for doing nothing. If he has no intention at all of allowing private patients to obtain drugs under the National Health Service, would it not be much more honest of him to say so, rather than to find one fresh excuse after another?

Mr. WALKER-SMITH: Discussions on administrative procedures were quite clearly made without commitment on the question of principle. On the question of principle, our position is that people have a right to resort to private practice if they so desire and, therefore, the preservation of private practice is a matter of concern to the Government. If the present position endangers the existence of private practice or prevents any substantial number of people availing themselves of it who would otherwise do so, we shall certainly consider the question of drugs. At the moment we have no evidence of that.

Dr. EDITH SUMMERSKILL: Is the Minister aware that his attitude is approved by many doctors in this country and also by the whole of the public? If he gives way to the pressure that is continually applied to him, he will in fact be establishing two classes of sick people in this country and he will undermine the National Health Service. Does he recognise that if he accepts the suggestion the drug bill will be increased tremendously?—Mr. WALKER-SMITH: I do not think that the word "pressure" is particularly felicitous to describe the conscientious efforts of some of my hon. Friends to put forward considerations in the public interest. I think that the principle is quite clear. People are entitled to resort to the National Health Service and all that goes with it. They are also entitled, if they so prefer, to go to private practice. It does not necessarily and logically follow that if they do the second they should have drugs on the same terms as the first. It is important to preserve the right of private practice and, therefore, if the evidence is forthcoming we shall certainly consider it, but so far the evidence has not been forthcoming.

Dr. JOHNSON: Is the Minister aware that many of those in private practice fear that their position as private practitioners is endangered by this? Is he also aware that at the outset of the National Health Service it was clearly stated then that all the service or any part of it is to be available to anyone in England and Wales, and does he not think that his present statement is contrary to the expression of intention?—Mr. WALKER-SMITH: I think not, because the provision of drugs is not a separate element but an ancillary part of the general-practitioner service. There is, of course, a wealth of assertion to the effect that private practice is endangered and people are debarred from entering into it who would otherwise do so, but as he knows there is a difference between assertion and evidence and it is the evidence for which we look to be supplied. The British Medical Association has ample opportunities to supply that evidence if it is available and I shall certainly consider it most carefully and sympathetically.

Mr. MAURICE EDELMAN asked the Minister whether he would invite the World Health Organisation to study the rise in the incidence of leukæmia in relation to man-made radiation.—Mr. WALKER-SMITH: I understand that there is already liaison between the World Health Organisation and the United Nations Scientific Committee on the Effects of Atomic Radiation, which has this subject under review.

Incidence of Leukæmia

Mr. EDELMAN: Has the attention of the Minister been drawn to the statement by the French High Commissioner for Atomic Energy that, as a result of the 1957-58 tests, 1000 people will die of leukæmia and 1000 children will be born deformed? Will he recall his own figures which show that since 1948 deaths in this country from leukæmia have risen from 1000 to over 2000 last year? Does not that indicate an association between leukæmia and man-made radiation? Will he draw the attention of Governments, now contemplating either making new tests or reinstating old tests, to the danger to public health from such nuclear tests?—Mr. WALKER-SMITH: The rise in the death-rate from leukæmia has been general in the world and has been going on for the past thirty years or so, long before these tests. This is, of course, an important subject and at the next session of the United Nations Committee there is to be further discussion of the connection between radiation and leukæmia. The nuclear aspect is relatively small compared with the natural background radiation and the radiation from medical and diagnostic radiology.

Mr. R. W. SORENSEN asked the Minister, as representing the Minister for Science, to what extent the increases of leukæmia of 26% in Essex, 59% in Cumberland, 39% in Cambridgeshire, 65% in Monmouth and Montgomeryshire, and 80% in Caernarvonshire since 1950 now indicate that radiostrontium fall-out is becoming serious.—Mr. WALKER-SMITH replied: My noble Friend is advised that it is highly unlikely that these changes can be attributed to radiostrontium fall-out. For some thirty years death-rates from leukæmia have been observed to be increasing in all countries where good records are kept, including the United Kingdom. Moreover, in small localities, where prevailing levels have been low, as in several of those counties mentioned, they would be expected to rise towards the national average.

1. See *Lancet*, Nov. 21, 1959, p. 906.

Hospital Building

Dr. BARNET STROSS asked the Minister of Health whether he was satisfied that the capital investment plans of the regional boards could be effectively carried out without a substantial increase in the staff concerned.—Mr. WALKER-SMITH replied: A considerable increase of staff, particularly architects, will be needed to implement the Government's increased programme of hospital building. I am discussing with regional hospital boards how additional architects might best be recruited and trained.

Compensation for Goodwill

Applications from about 100 doctors or their representatives have been refused on the ground that a claim was not made within the time-limit, which, after extension, finally expired on Feb. 28, 1951.

Medical Representation on R.H.B.s and H.M.C.s

The percentage of medical (including dental) representation on regional hospital boards ranges from 20·8 in the Leeds region to 32·7 in the North-East Metropolitan region. The average percentage of medical representation on hospital management committees ranges from 18·8 in the South-West Metropolitan region to 29 in the Sheffield region.

Obituary

FREDERICK CHURCHILL DAVIDSON

M.C., M.B. Edin., D.P.H.

Dr. Churchill Davidson died on Nov. 8 at his home in Camberley, Surrey, where he had been in practice for nearly 40 years.

He was born in 1889, the son of the Rev. R. Davidson of Montrose. He graduated at Edinburgh University in 1912 and joined the R.A.M.C. as a regular; and, as medical officer to the Cameronians, he was with the first draft to go overseas in 1914. He was one of the first doctors to be awarded the Military Cross, and he ultimately held the rank of colonel A.M.S.

In 1921 he took up general practice in Camberley and became medical officer of health to Frimley and Camberley urban district council. He is remembered as " a general practitioner of the very best type who kept himself well abreast of the times and, by his devotion to duty and absolute integrity, won the confidence and respect of his patients ". During the late war he was in charge of the surgical unit at Netley Hospital and also served in North Africa.

Dr. Churchill Davidson leaves a widow. Their three sons are all doctors, and two are on the staff of St. Thomas's Hospital.

Appointments

CHRISTIE, W. J., M.B. Glasg., D.P.H.: deputy physician-superintendent, Derwent Hospital and Draycott Hospital, Derby.
COLVIN, BEATRICE, M.R.C.S.: assistant M.O., Middlesex area (Wembley and Willesden).
DEAS, K. S., M.B. Edin., D.P.H.: district M.O.H., Lincolnshire (Spalding and East Elloe districts).
FRANCIS, H. W. S., M.B. Cantab., D.P.H.: deputy M.O.H., deputy principal school M.O., and deputy port M.O., Portsmouth.
LETHEM, J. E., M.B. Leeds: assistant M.O. (anæsthetist in school and maternity and child welfare dental services), Bradford.
MANGAN, MARY C., M.B. N.U.I.: assistant divisional M.O., Lancashire (Widnes and Whiston area).
RILEY, ESTHER T., M.B. Edin.: assistant M.O.H. and school M.O., West Bromwich.
TEMPOWSKI, W. J., M.B. N.U.I.: school M.O. and assistant M.O.H., Coventry.

Hertfordshire County Council:

BEARD, JESSIE M., M.B., B.SC. Manc.: assistant M.O.
BURGESS, NORA M., M.B. Glasg.: assistant M.O.
MARTIN, PATRICIA L., M.B. Punjab, D.OBST., D.P.H.: assistant M.O.
WRIGHT, ANNIE H., M.B. Glasg.: assistant M.O.

Leeds Regional Hospital Board:

DRANSFIELD, G. A., M.B. Lond., D.P.M.: consultant in psychiatry, Menston Hospital and associated general hospitals.
FORREST, A. D., M.D. St. And., M.R.C.P., D.P.M.: consultant in psychiatry, St. James's Hospital, Leeds.
WILKINSON, N. V., M.B. Durh., D.P.M.: consultant in psychiatry, Storthes Hall Hospital, Kirkburton, and associated general hospitals.

Diary of the Week

DEC. 6 TO 12

Monday, 7th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Prof. Sheila Sherlock: Portal Hypertension.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow, C.2
6 P.M. Prof. Charles Huggins (Chicago): Influence of Hormones on the Liver.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. M. G. Coyle: Placental Steroid Hormones.

Tuesday, 8th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. W. S. C. Copeman: The " Scientific " Basis of Tudor Medicine. (First of two FitzPatrick lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4 P.M. Dr. E. F. Scowen: Hormone Dependent Cancer, the Present Position. (Imperial Cancer Research Fund lecture.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Psychiatry.* Symposium on Salt and Water Metabolism in Relation to Psychiatry.
5.30 P.M. *Experimental Medicine and Therapeutics.* Dr. C. E. Ford: Chromosomes of Normal Somatic and Leukæmic Cells. Dr. D. G. Harnden: Abnormalities of Chromosome Constitution and Defects of Sex Development.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.1). Dr. L. G. Lajtha: Autoradiography in Bone-marrow Studies.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. E. H. Belcher: Functional Tests with Radioisotopes.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Aleck Bourne: Nutrition and Weight Gain in Pregnancy.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. W. N. Goldsmith: Acneiform Eruptions.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
5 P.M. Sir Francis Walshe: Evolution of Ideas in Neurology During the Past Century and the Future of Neurological Medicine. (First of three Harben lectures.)
MANCHESTER MEDICAL SOCIETY
5 P.M. (Clinical Sciences Building, York Place, Manchester.) *Surgery.* Prof. John Bruce: Surgery of Non-malignant Intestinal Disease.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Prof. Martin Roth: Problem of Mode of Action of Convulsive Treatment.

Wednesday, 9th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
2.30 P.M. Lord Cohen of Birkenhead: Reflections on Specialism in Medicine. (Watson-Jones lecture.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. J. D. N. Nabarro: Laboratory Investigations in Endocrinology.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. J. K. Clark (Philadelphia): Renal Excretion of Magnesium.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Cellular Nævi and Malignant Melanomata.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. Matthias Paneth: Surgery of Secundum Atrial Septal Defects.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P.M. Sir Francis Walshe: Evolution of Ideas in Neurology During the Past Century. (Second Harben lecture.)
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School University of Manchester.) *Pathology.* Dr. Fred Stratton: Advances in Blood-transfusion and Blood-groups.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW
5 P.M. Dr. Maurice Campbell: Surgical Treatment of Pulmonary Stenosis. (Walker lecture.)
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Queen's College Dundee.) Prof. James Walker: Maternal/Fœtal Respiratory Exchange.

Thursday, 10th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Dr. Copeman: Diagnosis, Disease, and Treatment in Tudor Times. (Last FitzPatrick lecture.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. H. H. Nixon: Experimental Study of Propulsion in Isolated Loops of Intestine and Application of the Findings in the Surgery of Neonatal Intestinal Obstruction. (Hunterian lecture.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. Dr. Sheila T. Callender: Iron Absorption.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. T. Alper, Dr. M. Ebert, Dr. R. H. Thomlinson: Biological Effects of Radiation.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. S. Pegum: Lichenoid Eruptions.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P.M. Sir Francis Walshe: Evolution of Ideas in Neurology During the Past Century. (Last Harben lecture.)
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Prof. A. W. Williams: Cardiovascular Disorders at an African Hospital in Uganda.
ALFRED ADLER MEDICAL SOCIETY
8 P.M. (1, Wimpole Street, W.1.) Dr. W. L. Neustatter: Dangerous Depressives.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh, 8.) Dr. Denis Melrose: Present Status of Open Heart Surgery.

Friday, 11th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Prof. C. A. Wells: Intestinal Loops in Urology and Gastric Surgery.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Dr. Imrich Friedmann: Chemotherapy.
5.30 P.M. Mr. C. Gill-Carey: Surgery of the Nasal Septum.

Notes and News

HOSPITAL COSTING RETURNS

SINCE 1957, 250 large hospitals in England and Wales have used a detailed system of hospital costing which shows the cost of different departments. The second report [1] based on returns collected under this system includes cost statements for wards, outpatients (including casualty) departments, and 11 other departments, such as diagnostic X-ray, pathological laboratories, catering, and boiler-house. The average cost per inpatient week in a non-teaching hospital ranged from £27 5*s*. 4*d*. in the South Western region to £19 14*s*. 1*d*. in the Liverpool region. The national average was £23 14*s*. 5*d*., compared with £22 6*s*. 2*d*. in 1957–58. The average cost for a London teaching hospital was £34 13*s*. 6*d*. (£33 11*s*. 3*d*. in 1957–58) and for a provincial teaching hospital £29 9*s*. 2*d*. (£28 4*s*. 6*d*. in 1957–58). In a circular to hospital authorities [2] the Minister of Health says that the first returns under the new system published last year have already given useful indications for possible economies and improvements. The most "immediately fruitful" was the information about boiler-houses, power, lighting and heating, laundry, and catering.

University of London

At recent examinations for the D.P.M. the following were successful:

R. H. Culpan, C. M. Parkes, G. K. M. Shaw.

University of Birmingham

Dr. B. S. B. Wood has been appointed part-time lecturer in pædiatrics and child health.

University of Edinburgh

Dr. J. S. Munro has been appointed part-time lecturer in the general-practice teaching unit.

Royal College of Obstetricians and Gynæcologists

At a meeting of the council on Nov. 28 with Prof. A. M. Claye, the president, in the chair, Mr. David Hay and Mr. Ian MacGillvray were appointed William Blair-Bell lecturers for 1960, Dr. Landrum Shettles (New York) Green-Armytage lecturer, and Dr. T. F. Corkill (Wellington, New Zealand) William Meredith Fletcher Shaw lecturer. The Edgar-Gentilli prize was awarded to Dr. W. Park and Dr. B. M. Hobson.

Royal Society of Medicine

Section of Anæsthetics.—This section is offering a prize of £30 for the best paper written by a doctor in the National Health Service holding a clinical appointment in anæsthesia. Further particulars may be had from the hon. secretary of the section, 1, Wimpole Street, London, W.1.

Royal Society

At the anniversary meeting of this society on Nov. 30, Sir Cyril Hinshelwood was re-elected president. Re-elections of medical fellows included Sir Lindor Brown as biological secretary and Prof. Wilson Smith as a member of the council.

Plans for Amalgamation of Spastics Organisations

The National Spastics Society and the British Council for the Welfare of Spastics are planning to merge their organisations, and have issued the following joint announcement:

"Joint informal discussions started some months ago and a formal joint committee has now been set up to prepare detailed plans. The two executive committees are satisfied in principle that amalgamation is desirable and it is expected that a formal merging will take place in the course of the next year after detailed proposals have been prepared, and approved by the members of both bodies. Though both organisations have made very great progress in recent years in the work of treatment, education and care of spastics there is still a tremendous national programme to be carried out. It is considered that this programme, with its plans for major extension of research work, can best be advanced by combining the resources of the two bodies."

1. National Health Service: Hospital Costing Returns Year Ended March 31, 1959. Vol. 1: hospitals which operated the main scheme. H.M. Stationery Office. £1 15*s*.
2. H.M.(59)101.

Welsh National School of Medicine

Dr. A. L. Cochrane, a member of the Medical Research Council's Pneumoconiosis Research Unit at Cardiff, has been appointed David Davies professor of the department of tuberculosis and chest diseases in the school.

Dr. Cochrane, who is 50, was educated at Uppingham and at King's College, Cambridge, where he took a first in both parts of the natural sciences tripos. His clinical studies, in Vienna and at University College Hospital, were interrupted by service in the British Ambulance Unit in the Spanish war, but he qualified in 1938. Having later joined the Army, he was taken prisoner in Crete in 1941 and spent four years in Germany, where he had care of many tuberculous prisoners, chiefly Russian and French, and developed his interest in research aspects of preventive medicine. For this work he was appointed M.B.E. With a Rockefeller fellowship he spent eighteen months at the Henry Phipps Institute, Philadelphia, before joining the M.R.C. pneumoconiosis unit. In the unit he worked at first on the development of radiological and epidemiological techniques for studying pneumoconiosis and tuberculosis—making valuable observations, incidentally, on "observer error" in taking histories and in reading X-ray films. Later he applied the epidemiological techniques to other conditions, including bronchitis, hypertension, and mental disorder, and he has thus pioneered the use of "defined communities" in the study of a wide variety of medical problems. In his new post he will be able to continue his epidemiological work with the unit, which will now be brought into closer relation with the university.

Mental Health Survey in Anglesey

At the request of the Anglesey County Council the Nuffield Provincial Hospitals' Trust has agreed to set aside £13,700 to finance a survey of mental health needs in Anglesey. The survey, which is expected to take two to three years, is intended to provide factual information on which to plan the development of mental health services for the community and to include a research project into selected aspects of mental disorder. The departments of psychological medicine (Dr. S. Barton Hall) and social science (Prof. T. S. Simey) of the University of Liverpool, have agreed to help in the conduct of the survey.

Training in Hospital Administration

Applications for a further 16 training posts for prospective hospital administrators are invited by the Minister of Health and the Secretary of State for Scotland under the National Recruitment and Training Scheme begun in 1956.

The posts are open both to young officers already employed in the National Health Service and to graduates and professionally qualified people who wish to make hospital administration their career. They are tenable for three years beginning in October, 1960. The normal age-limit is 30, though candidates up to the age of 35 may be considered. During their training the student administrators will be given practical experience of hospital administration with different hospital authorities and will attend courses at the Hospital Administrative Staff College of the King Edward's Hospital Fund for London or at the University of Manchester. Their fees will be paid and they will receive a salary beginning at £575. There are at present 40 candidates undergoing training, 3 of them women. Most of the first group of trainees have already obtained permanent posts in the hospital service.

Mr. L. N. Pyrah has been awarded the St. Peter's medal of the British Association of Urological Surgeons.

Dr. Cicely Williams has been appointed visiting professor of maternal and child health in the American University of Beirut.

On Tuesday, Dec. 15, at 8.15 P.M., at the Royal College of Nursing, Henrietta Place, W.1, the Osler Club of London is holding a meeting to commemorate the centenary of the publication of Florence Nightingale's *Notes on Nursing*.

The Hospitals' Symphony Orchestra is holding a concert today, Saturday, Dec. 5, at 8 P.M., at Duke's Hall, Royal Academy of Music, Marylebone Road, London, N.W.1. Admission is by programme (4*s*.).

CORRIGENDUM: *Fibrocystic Disease of the Pancreas.*—In last week's leading article (p. 955) the penultimate sentence in col. 1 should have opened: "Stimulated by the work of Pauling's group, Ingram, and others,[15–17] those investigators who think in terms of 'molecular diseases' now look on mucoviscidosis . . ."